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Archives of Dermatology and Syphilology

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LINEAR SCLERODERMA

Association With Abnormalities of the Spine and Nervous System

LOUIS RUBIN, M.D.
CHICAGO

THE CAUSE of linear scleroderma is obscure. Several authors have been impressed by the fact that many lesions in this disease have a segmental distribution or follow the course of peripheral nerves. Therefore, they have assumed that linear scleroderma originates in the nervous system.[1] In support of the neurogenic theory are observations in cases in which the development of linear scleroderma followed nerve injury; for instance, the case of Kingery[2] in which, following block anesthesia of the mandibular nerve, a sclerodermatic lesion developed in the supply area of this nerve. Bettman,[3] however, interpreted linear scleroderma as a developmental anomaly independent of the nervous system and rather analogous to nevi, because he observed a striking similarity in the patterns of unilateral linear nevi and linear scleroderma.

The following report is based on the observations in 13 unselected cases of linear scleroderma. All the patients were seen in the University of Chicago clinics during the fifteen year period prior to writing. Analysis of the observations in these patients will point more clearly toward the neurogenic causation of this entity.

REPORT OF CASES

For the sake of brevity the pertinent data of the cases are summarized in table form. The localization, extent and shape of lesions are repre-

From the Section of Dermatology, Department of Medicine, University of Chicago (Chief of Service, Dr. Stephen Rothman).

1. Becker, S. W., and Obermeyer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947, p. 306. Vohwinkel, K. H.: Zur Pathogenese der Sklerodermie, Arch. f. Dermat. u. Syph. **158**:28, 1929. For older literature see Cassirer, R.: Die Vasomotorisch-trophischen Neurosen, ed. 2, Berlin, S. Karger, 1912, p. 588.

2. Kingery, L. B.: Scleroderma Following Nerve Injury, Arch. Dermat. & Syph. **5**:579 (May) 1922.

3. Bettmann, S.: Bandförmige Sklerodermie und Naevuszeichnung, Arch. f. Dermat. u. Syph. **142**:235, 1923.

sented diagrammatically, showing the spinal root zones.[4] Description of the clinical appearance of the lesions is omitted. All lesions were clinically typical of linear scleroderma, and this diagnosis was confirmed histologically in cases 1, 2, 3, 4, 7, 11 and 13. In the following descriptions, only a few additional data are mentioned which could not be included in the table.

CASE 1.—The spiral lesion on the left leg followed fairly closely what was shown by Brain[5] and Ranson[6] to be the border between cutaneous areas of distribution of the second and third lumbar spinal root zones. This might well represent the overlap area of these two segments. The lesion followed the course of no single cutaneous nerve, but cut across areas supplied by the lateral cutaneous nerve of the thigh and the intermediate and medial cutaneous rami of the femoral nerve, all of which originate in the lumbar plexus. Therefore, it seems that if this

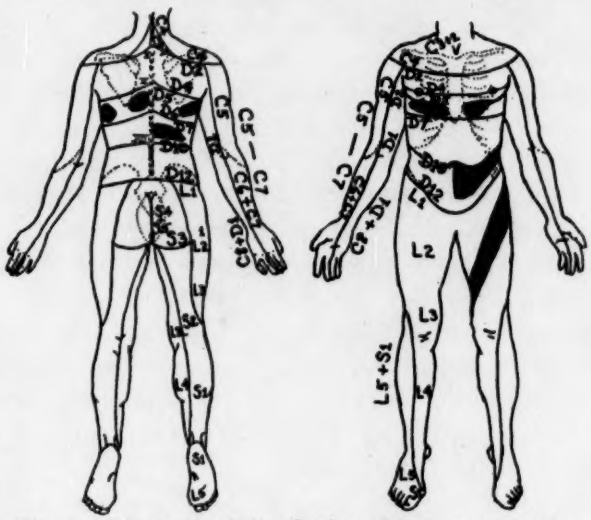

Fig. 1.—Diagrams of distribution of lesions (case 1).

lesion had anything to do with the nervous system, it was of central rather than peripheral origin and its segmental spiral distribution was determined by the embryonic rotation of the lower limb bud.

The lesion on the left lower aspect of the abdomen terminated rather sharply at the midline, and its upper border, beginning medially at the umbilicus, curved as it moved laterally as is usually shown in textbooks for the border between the

4. Diagrams showing the cutaneous distribution of spinal root zones or segments and the areas of distribution of cutaneous nerves vary considerably in the works of different authors. In these case reports a simplified diagram of segmentary distribution which is used in the University of Chicago clinics was chosen on which to overlay the lesions.

5. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940, p. 28.

6. Ranson, S. W.: The Anatomy of the Nervous System from the Standpoint of Development and Function, ed. 6, Philadelphia, W. B. Saunders Company, 1939, p. 63.

ninth and tenth thoracic spinal root zones. The lesions on the chest and the back were somewhat symmetrically placed; some ran parallel to the long axis of spinal root zones.

CASE 2.—The upper portion of the lesion in this case practically duplicated the lesion of the leg in the first case. However, the lower portion extended into the fourth lumbar spinal root zone. The lesion did not follow the course of any single peripheral nerve. If the origin of this lesion were in a peripheral nerve trunk, it should be expected that in the distal portion it would involve most of the cutaneous distribution of some branch of the mother nerve. If central origin is assumed, it is understandable that only a few fibers of several peripheral nerves were involved according to their spinal root origin. There was a history of mild trauma to the sacral region one and one-half years previous to the onset of the lesion.

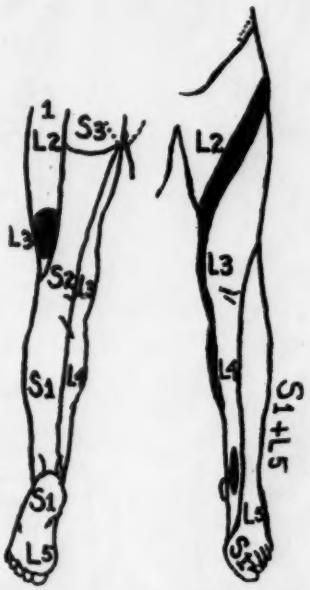

Fig. 2.—Diagram of distribution of lesions (case 2).

CASE 3.—The distribution in the lower extremities, as seen in cases 1 and 2, was rather accurately reproduced in this case except that part of the first lumbar root zone was also involved in the inguinal region. The lesions of the shoulders and arms filled much of the zones supplied by the fourth and fifth cervical roots and involved parts of some of the upper thoracic roots. In fact, the lower borders of the lesions of the arm closely simulated the lower borders of the fifth cervical root distribution as frequently pictured. The symmetry of these lesions is striking.

CASE 4.—In this case again no definite peripheral nerve distribution could be made out, but part of practically every spinal root zone from the tenth thoracic to the third sacral root zone was involved. The buttock involvement ended medially rather sharply at the lateral edge of the fourth and fifth sacral root zones, and the abdominal lesion ended at the paramedian line.

CASE 5.—The lesions in this case had a distribution somewhat different from that in the previous cases. They lay within the second lumbar through the first

sacral root zones. According to the diagrams of Holmes[7] the lesions were principally in the fourth lumbar zone. The abdominal lesions, which were on the opposite half of the body, were in the ninth and tenth thoracic root areas. Although the lesions did not fill the area of any single peripheral nerve or its

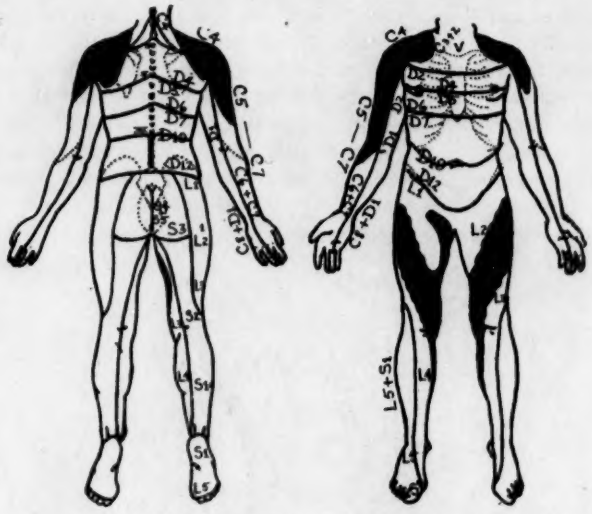

Fig. 3.—Diagrams of distribution of lesions (case 3).

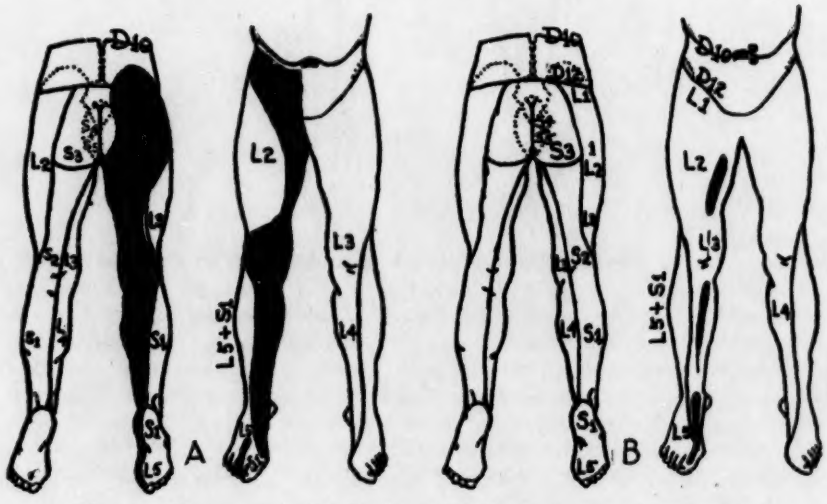

Fig. 4.—Diagrams of distribution of lesions: *A*, case 4; *B*, case 5.

branches, it should be stated that they lay within the supply areas of the intermediate and medial cutaneous rami and the long saphenous nerve, which are branches of the femoral nerve.

7. Holmes, G.: Introduction to Clinical Neurology, Edinburgh, E. & S. Livingstone, 1946, p. 75.

CASE 6.—The area of the lesion in this case was similar to that in the preceding one, except that it is more accurately confined to Holmes's fourth lumbar zone.

CASE 7.—The lesions in this case were within the second lumbar through the second sacral root zones except for the abdominal lesion, which was approximately in the ninth thoracic zone or in the overlap area of the ninth and tenth

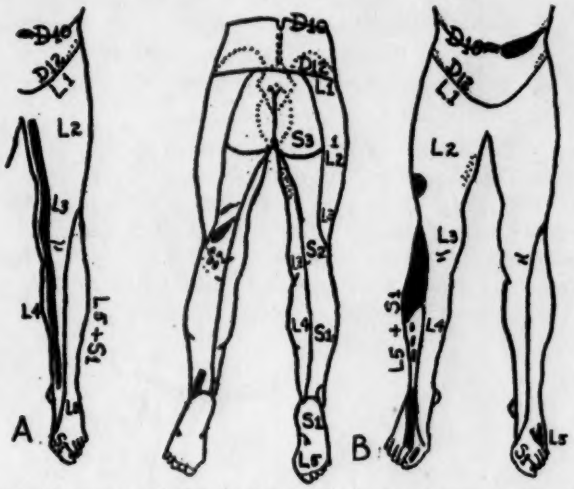

Fig. 5.—Diagrams of distribution of lesions: *A*, case 6; *B*, case 7.

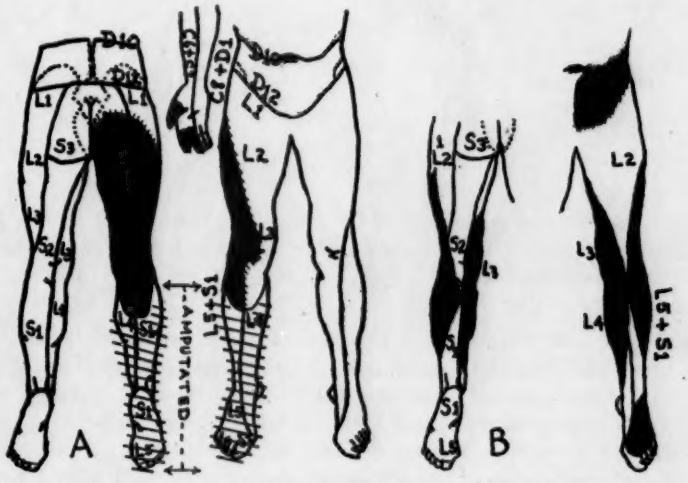

Fig. 6.—Diagrams of distribution of lesions: *A*, case 8; *B*, case 9.

thoracic zones. Single nerve distributions for the lesions of the leg in this case, too, were difficult to determine.

CASE 8.—(The diagram is schematic and made from photographs. The patient was not seen by me.) When the patient was 2 years and 9 months of age limping of the right leg was first noted, and shortly thereafter shortening of this

leg, associated with hardening of the skin and muscles up to the hip, became apparent. Amputation of the right leg below the knee was done when the patient was 14 years old. During the hospitalization for amputation there was noted wasting of the first three fingers of the right hand, with the appearance of a linear scar on the third finger and contraction deformity of these fingers in flexion. Generalized weakness of the right hand and forearm was present. Talipes cavus of the left foot was also noted.

Exact outlining of the lesion of the leg could not be made. From previous description and clinical photographs after amputation, it was judged that the lesion of the leg involved the first lumbar through the fifth sacral segments. The lesion of the hand apparently involved the area of distribution of the median nerve.

Case 9.—(The diagram is schematic, made from the record and a rough drawing therein. The patient was not seen by me.) When the patient was 3 years old there was first noted an area of shiny skin about the left knee, which had increased to cover most of the leg by the time the patient was 6½ years old.

The examiner described a "defect in bodies of the second, third and fourth sacral vertebrae" and made a diagnosis of spina bifida occulta. I was unable to find this patient to get roentgenographic verification of the diagnosis.

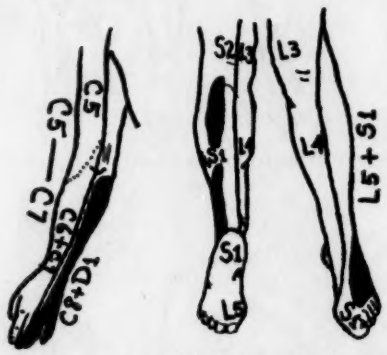

Fig. 7.—Diagram of distribution of lesions (case 10).

Several adjacent spinal root zones seemed to be involved in this case also. The absence of deep reflexes could possibly be accounted for on the basis of the contractures or muscle atrophy, but the "foot-slapping" gait indicated possible neurogenic origin.

Case 10.—At 2 years and 9 months of age the patient fell down a flight of stairs, but was apparently uninjured. A few days later swelling of the back of the left hand appeared and persisted for about two weeks, after which the skin in that region became white and glossy. This change gradually spread to the wrist and up the posterior ulnar aspect of the left forearm. At 4 years of age a similar change appeared on the superior aspect of the left foot and on the posterior aspect of the left calf. I first saw the patient when she was 8 years and 6 months of age, at which time the parents stated that the lesions had improved somewhat.

The lesion of the hand and arm, with its onset so closely following trauma and its distribution and symptoms so accurately simulating an ulnar nerve or brachial plexus syndrome, probably was due to peripheral nerve injury at the time of the fall.

The lesion of the foot and leg, beginning well over a year after the fall and not following the course of a single nerve but falling in areas of adjacent nerve roots, cannot be attributed to peripheral trauma, but was more likely due to a local pathologic condition associated with the spina bifida occulta.

CASE 11.—(The diagram was drawn from photographs. The patient was not seen by me.) At 38 years of age the patient first noticed thickening and wrinkling of the skin on the medial aspect of the right upper arm. Within five months the process extended in a bandlike manner and spiral path to the extent shown in the diagrams. Cordlike folds, which interfered with complete extension of the elbow, developed in the antecubital space. During the development of the lesions, transitory numbness and tingling were present in the entire right side of the body.

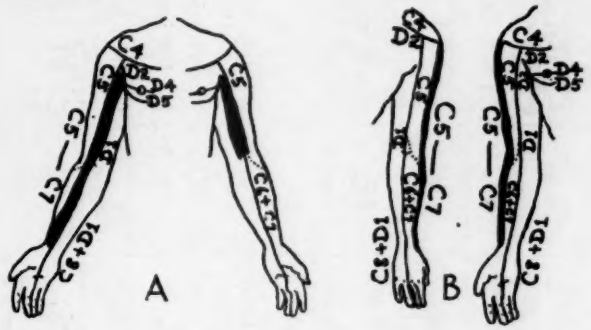

Fig. 8.—Diagrams of distribution of lesions: *A*, case 11; *B*, case 12.

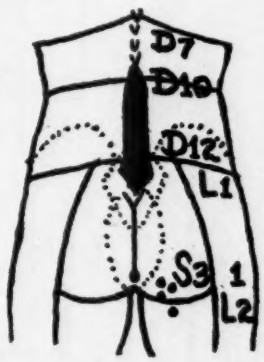

Fig. 9.—Diagram of distribution of lesions (case 13).

CASE 12.—(The diagram is schematic. The patient was not seen by me.) The lesion did not follow the course of any peripheral nerve but lay in the fifth and sixth cervical root zones of Ranson,[6] or fairly accurately and completely filled the fifth cervical area as mapped by Holmes.[7]

CASE 13.—At 47 years of age this patient was struck by an automobile. Roentgenograms at that time showed flattening of the ninth thoracic vertebra and a questionable fracture of the right transverse process of the fourth lumbar vertebra. She recovered and was asymptomatic until the age of 50, when pruritus developed in the spinal area at about the level of the eleventh thoracic vertebra.

Summary of Data in the 13 Cases Presented

Case No.	Sex	Age of Onset	Sites	Roentgenologic Observations	Age Roentgenograms Taken	Spinal Root Zones Involved by Lesions	Associated Clinical Observations and Comment
1	M	20	Abdomen, back, chest and leg (bilateral with some symmetry on back and chest)	Asymmetry of laminas (S-1)	29 yr.	D-5, D-6, D-7, D-9, D-10, D-11, D-12, L-2, L-3	Linear scleroderma plus morphea
2	F	4 yr. 8 mo.	Leg	Spina bifida occulta (S-1 and S-2)	5 yr. 2 mo.	L-2, L-3, L-4	
3	M	6 mo.	Shoulders, arms and legs (bilateral, symmetric)	Spina bifida occulta (S-1)	8 yr. 2 mo.	C-4, C-5, D-2, D-3, D-4, L-1, L-2, L-3, L-4	Flexion contracture, right elbow
4	F	4 yr. 5 mo.	Abdomen, buttock and leg	Spina bifida occulta (S-2, S-3 and S-4)	4 yr. 9 mo.	D-10, D-11, D-12, L-1, L-2, L-3, L-4, L-5, S-1, S-2, S-3	Equinovarus deformity of homolateral foot and flexion contracture of knee; decreased volume of leg; atrophy of gluteal region; prominent veins
				Sacral part of spine normal	6 yr.		
5	M	3 yr. 6 mo.	Leg, abdomen (bilateral)	Spina bifida occulta (S-1, S-2 and S-3)	7 yr. 8 mo.	L-2, L-3, L-4, L-5, S-1	Pes cavus of homolateral foot; muscle fibrosis; ulcer of toe; right foot 2 cm. shorter than left; linear scleroderma plus morphea
6	F	22	Leg	Spina bifida occulta (S-1); asymmetry of laminas; prespondylolisthesis	55 yr.	L-2, L-3, L-4	Muscular atrophy of leg; prominent veins in lesion
7	F	6 yr. 8 mo.	Legs and abdomen (bilateral and some symmetry)	Spina bifida occulta	7 yr. 10 mo.	D-9, D-10, L-2, L-3, L-4, L-5, S-1, S-2	Linear scleroderma plus morphea
8	F	2 yr. 9 mo.	Leg and buttock	Spina bifida occulta (S-1); incomplete lumbarization of left transverse process of S-1	19 yr.	L-1, L-2, L-3, L-4, L-5, S-1, S-2, S-3, S-4, S-5	Pes cavus of heterolateral foot
		14 yr.	Hand	No roentgenogram of cervical part of spine		C-6, C-7	Flexion contracture and weakness of hand
9	F	3 yr.	Leg and abdomen	No roentgenogram; clinically spina bifida occulta (S-2, S-3 and S-4)	None: examined at age of 6½ yr.	D-10, D-11, D-12, L-1, L-2, L-3, L-4, L-5, S-1	Contracture deformity of homolateral knee; atrophy of leg; "foot-slapping" gait; deep reflexes in leg absent

Case No.	Sex	Age of Onset	Sites	Roentgenologic Observations	Age Roentgenograms Taken	Spinal Root Zones Involved by Lesions	Associated Clinical Observations and Comment
10	F	2 yr. 9 mo.	Arm	Spina bifida occulta (S-2)	4 yr. 6 mo.	C-8, D-1	Trauma at 2 yr. 9 mo.; ulnar deviation of left hand; weakness of flexion of fourth and fifth fingers; decreased volume of affected areas
		4 yr.	Leg	Lumbosacral part of spine normal; cervical part of spine normal	8 yr. 6 mo.	L-5, S-1	
11	F	38 yr.	Arms (bilateral, symmetric)	Forked spinous processes (C-4, C-5 and C-6); osteoarthritis lower cervical part of vertebrae	38 yr.	C-5, C-6, C-7, C-8, D-1, D-2	Slight flexion contraction of right elbow, paresthesias of right side
12	F	6 yr.	Arm	No clinical or roentgenographic examination of the spine		C-5, C-6	
13	F	50 yr.	Lower part of spine	Compression fracture (L-2); flattening (T-9); fracture transverse process (L-4); osteoarthritis	47 yr. 50 yr.	D-10, D-11, D-12, L-1, L-2, L-3, L-4	Trauma at 47 yr.; linear scleroderma plus morphea

Two months later there was a pigmented and depigmented thickened scaling firm band, about 5 cm. wide, extending in the midline from the tenth thoracic vertebra to the sacrum. On the right buttock were four depigmented atrophic spots, each measuring about 1 cm. in diameter.

Recent roentgenograms showed a compression fracture of the body of the second lumbar vertebra, with localized osteoarthritic changes. There was minimal osteoarthritis and scoliosis of the dorsal aspect of the spine.

This patient had a midline lesion in the area of the spine following direct trauma to the spine which resulted in fractures and localized osteoarthritis. Interestingly, Pritchard[8] presented a diagram of the cutaneous distribution of the spinal root zones which showed a central overlap of the first through the fourth lumbar over the tenth through the twelfth thoracic spinal root zones in the area of this patient's lesion.

These patients all had roentgenograms of the chest, serologic tests for syphilis, blood cell counts and urinalyses, the results of all of which were normal. In some cases tests of basal metabolism, tuberculin patch tests, serum calcium estimations and other special studies were done, and all yielded normal results.[9]

ANALYSIS OF DATA

A. Localization on Lower Extremities.—Analysis of the foregoing data shows that 10 of the 13 patients had lesions of one or both lower extremities. Five of these 10 patients also had lesions on the abdomen, and 2 of these showed involvement of a buttock.

None of the lesions of the leg closely followed the distribution of a peripheral nerve, but all seemed to be distributed longitudinally in the long axis of one or several spinal root zones.

Six of the 10 patients had roentgenographic evidence of varying degrees of spina bifida occulta at an age when closure of the neural arch is usually completed, and 1 patient, for whom roentgenographic examination was not done, presented clinical evidence of severe spina bifida occulta. Thus, 70 per cent of the patients with scleroderma of the legs, lower part of the abdomen or buttocks had spina bifida occulta. Two of the 3 adults in this group had definite spina bifida occulta of the first sacral vertebra. In addition, 1 showed decided asymmetry of the laminas of one sacral vertebra, another had prespondylolisthesis, and a third had incomplete lumbarization of the left transverse process of the first sacral vertebra.

Seven (70 per cent) of the patients were female and 3 (30 per cent) were male.

The average age of onset in this group was 7.15 years. This figure, however, may be misleading, for 8 of the patients were under 7 years of age at the onset of the disease and 2 were 20 and 22 years of age, respectively. The average age of onset for the 8 patients under 7 years was 3.7

years. Even this average results from 7 cases in which the onset was below the age of 4 years and 8 months and 1 case in which the onset was at 6 years and 8 months. Thus, onset below the age of 5 years seems to be predominant. The significance of this early onset and the explanation of exceptionally late onset will be further elucidated in the comment.

B. Localization on Upper Extremities.—Five of the 13 patients had lesions of one or both upper extremities. Three of these patients also had lesions elsewhere on the body. Some of the lesions of the upper extremities (cases 3, 11 and 12) were distributed parallel to the long axes of adjacent spinal root zones. However, one of the arm lesions (case 10) closely simulated the distribution and symptoms of an ulnar nerve or lower brachial plexus syndrome. In this case, the onset of the cutaneous change was preceded by trauma and the history strongly suggested that peripheral nerve injury played a role in the development of this linear scleroderma lesion. In keeping with the assumption of peripheral origin, roentgenograms of the cervical aspect of the spine showed no abnormalities in this case. In another lesion of the upper extremity (case 8) a median nerve syndrome was simulated. No history of peripheral trauma was elicited here, and roentgenograms of the cervical aspect of the spine were not available. In case 12 no clinical or roentgenographic examination of the spine was recorded. Of the remaining 2 patients with lesions of the arm, both had bilateral and remarkably symmetric lesions. In 1 (case 3), the anteroposterior and lateral views of the cervical aspect of the spine showed no abnormalities and there was no evidence of cervical ribs. In the other (case 11), the forked spinous processes of several cervical vertebrae probably were without any pathologic significance, these changes being extremely common in normal persons. On the other hand, this same patient showed some osteoarthritis of the lower cervical vertebrae, a rather uncommon observation in a person 38 years of age. Pressure effects on nerves or nervous tissue due to this hypertrophic process might well account for the symptoms.

Omitting the patient with osteoarthritis and the patient with obvious trauma, the average age of onset of the lesions of the arm was 6.8 years.

C. Localization on the Midline of the Back.—The disease in the remaining case to be considered (case 13) was clinically and histologically typical of scleroderma The onset was at a relatively late age, but the history of trauma was definite and the resultant abnormalities of the spine were obvious. The lesion is definitely related spatially to the overlap area of Pritchard.[8] However, it should be stated that illustrations of other authors do not show this overlap.

8. Pritchard, E. A. B.: Aids to Neurology, London, Baillière, Tindall & Cox, 1941, p. 123.

COMMENT

The diagrams indicate that in the majority of cases the lesions lay in the long axis of spinal root zones In some cases only adjacent zones were involved; in others, however, zones were skipped, and in some lesions the relation to segmentary distribution is debatable.

More significant than the spatial distribution, for the assumption of neurogenic origin of linear scleroderma, is the high incidence of spina bifida occulta in cases with lesions of the lower extremities.

Results of studies to determine the frequency of spina bifida occulta in normal persons show wide variations. Figures for the presence of this anomaly in the fifth lumbar vertebra vary from 1.2 per cent[10] to 2.3 per cent.[11] None in my series of 10 patients with linear scleroderma of the lower extremities showed such a defect.

Figures for the occurrence of spina bifida occulta in the combined lumbosacral aspect of the spine vary from 17.3 per cent[12] to 33 per cent,[13] and Schmorl[14] gave the results of several investigators who observed an incidence in the sacral aspect of the spine alone varying from 11 to 24 per cent. Despite these large variations, none of the figures approach the incidence of 70 per cent observed in the patients presented in this paper.

One must consider the age at which these defects are detected, for spina bifida occulta is much more frequent in young children. Hodges

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9. Five of the patients described in this survey have been presented before the Chicago Dermatological Society. These case presentations and discussions have appeared in the literature as follows: Rothman, S., and Felsher, Z.: Circumscribed Scleroderma, Arch. Dermat & Syph. **51**:77 (Jan.) 1945 (case 1). Rothman, S., and Shapiro, A. L.: Linear Scleroderma, ibid. **53**:199 (Feb.) 1946 (case 3). Rothman, S., and Krysa, H.: Linear Scleroderma with Spina Bifida, ibid. **55**:130 (Jan.) 1947; Linear Scleroderma ibid., to be published (case 7). Rothman, S., and Henningsen, A. B.: Linear Scleroderma, Following the Course of Nerves, with Muscular Atrophy, ibid. **50**:59 (July) 1944 (case 10).

10. Willis, T. A.: An Analysis of Vertebral Anomalies, Am. J. Surg. **6**:163 (Feb.) 1929.

11. Wheeler, T.: Variability in the Spinal Column as Regards Defective Neural Arches, Publication 30, Carnegie Institution of Washington, 1941.

12. Bohart, W. H.: Anatomic Variations and Anomalies of the Spine: Relation to Prognosis and Length of Disability, J. A. M. A. **92**:698 (March 2) 1929. Cushway, B. C., and Maier, R. J.: Routine Examinations of the Spine for Industrial Employees, ibid. **92**:701 (March 2) 1929.

13. Roederer, C., and Lagrot, F.: Le diagnostic radiologique du spina bifida occulta lombosacré, J. de radiol. et d'électrol. **10**:255, 1926.

14. Junghanns, H.: Die gesunde und kranke Wirbelsäule in Röntgenbild, in Schmorl, G.: Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern, Leipzig, Georg Thieme, 1932, pp. 195-199.

and his co-workers[15] showed the fusion of sacral arches to be normally completed during the fifth year and the order of fusion to be second, first, fourth and third sacral arches, respectively. In 8 of the 9 patients with lesions of the leg of whom I have roentgenograms, the final roentgenographic study was made after they were 6 years of age. The ages at examination varied from 6 years to 55 years.

Three (cases 1, 4 and 10) of the 10 patients with linear scleroderma of the lower extremities were considered not to have spina bifida occulta. Two patients had roentgenograms made when they were between 4 and 5 years of age which showed failure of fusion of the laminas of the second sacral vertebra. Fusion was observed to be complete when a second series of roentgenograms was taken at 8 years and 6 months of age. In a strict sense, the spina bifida occulta in this case has to be regarded as physiologic. However, the observations even in these cases may be significant, because the second sacral arch is normally the first to fuse. If one regards the observation of spina bifida occulta in these patients as significant, the percentage of spina bifida occulta in this series of patients with lesions of the lower extremity increases from 70 per cent to 90 per cent.

The preceding data indicate that spina bifida occulta is significant in linear scleroderma of the lower extremities.

There has been lack of agreement as to the clinical significance of spina bifida occulta, but it has been shown that it is related to several clinical conditions. Most important of these are deformities of the feet, principally clubfoot and hollow foot. In 3 of the cases presented there was seen one or the other of these deformities of the homolateral or heterolateral foot. Paralyses of different degrees of severity are sometimes seen with spina bifida occulta, and it should be pointed out that Money[16] and others[17] have reported sclerodermatous lesions occurring in patients with spinal paralyses. Flexion contractures of the knees have also been reported to be associated with spina bifida occulta, and this was noted in 2 of my patients. In addition, 2 with lesions of the arm, showed contractures. Queyrat and his co-workers[18] described trophedema of

15. Hodges, P. C.; Phemister, D. B., and Brunschwig, A.: The Roentgen-Ray Diagnosis of Diseases of the Bones and Joints, New York, Thos. Nelson & Sons, 1938, chart, p. 14.

16. Money, A.: Chronic Infantile Sclerema and Paralysis, Lancet **2**:811, 1888.

17. Dinkler, M.: Zur Lehre von der Sclerodermie, Deutsches Arch. f. klin. Med. **48**:514, 1891. Cockayne, E. A.: Congenital and Acquired Scleroderma in Childhood, Brit. J. Child. Dis. **13**:225 (Aug.) 1916.

18. Léri, A., and Engelhard: Trophoedème chronique et spina bifida occulta, Bull. et mém Soc. d. hôp. de Paris **44**:1169 (July 30) 1920. Queyrat; Léri, A., and Engelhard: Lésion cutanée rappelant la sclérodermie en bandes et spina bifida occulte, ibid. **45**:437 (March 18) 1921.

the lower extremity in a patient with spina bifida occulta and stated that the spinal defect may be an indication of "meningomedulloradicular" lesions, on which depend important "trophic" disturbances of the extremities.

Obviously, spina bifida occulta in itself is not enough to cause "trophic" disturbances. However, commonly the osseous anomaly is associated with pathologic conditions of the meninges and the cord. The observations of von Recklinghausen,[19] and more recently of Christopher[20] and Brickner,[21] indicate that in spina bifida occulta the nerve fibers of the cauda equina may be adherent to the superficial structures or that there may be pressure on the cord at the point of the spinal defect. Brickner enumerated the following various conditions which may accompany spina bifida occulta and cause remote neuromuscular symptoms: a distinct meningocele protruding through the bony cleft, a closure of the cleft by a tough membrane adherent to the skin, the perforation of the membrane by a dense band attached to the subcutaneous tissue externally and compressing the cord structures internally, fat tissue lying within the canal concealed by this membrane, a bulging of the dura mater, an exostosis within the canal compressing the cord structures and a myofibrolipoma extending through the cleft into the bony canal and compressing the cord and its roots or causing a degeneration of the cord tracts themselves. If one realizes the great variety of these associated phenomena, it becomes understandable that in some cases spina bifida occulta will not cause demonstrable pathologic changes, whereas in other cases it will be associated with severe "trophic" disturbances. The type, localization and extent of the lesion of the cord or spinal root will determine the type, localization, extent and unilaterality or symmetry of the "trophic" lesions.

A possibly important mechanical factor in the development of "trophic" disturbances is the differential rate of growth of the spinal column and the spinal cord. In early intrauterine life, the cord fills the canal and the nerve roots emerge from the canal horizontally, whereas in adult life, the cord is only two thirds as long as the canal and the nerve roots have necessarily lengthened. According to Caffey,[22] the rate of lengthening of the spinal column is greatest during the first two

19. von Recklinghausen, F.: Untersuchungen über die Spina bifida, Virchows Arch. f. path. Anat. **105**:243, 1886.

20. Christopher, F.: Spina Bifida Occulta, with Report of a Case, Internat. Abstr. Surg. **33**:1 (July) 1921.

21. Brickner, W. M.: Spina Bifida Occulta, Am. J. M. Sc. **155**:473 (April) 1918.

22. Caffey, J.: Pediatric X-Ray Diagnosis: A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology, Chicago, The Year Book Publishers, Inc., 1945, p. 784.

years and the increase is greatest in the lumbar aspect of the spine. In case of developmental anomalies as previously listed, abnormal tension on nervous structures will be greatest during the first two years. Allowing some time for the development of "trophic" changes, this fact seems to be in keeping with the early age of onset of linear scleroderma. On the other hand, the final length of the spine is not attained until between the twenty-second and the twenty-fourth year, which explains the cases in which the disease started not in early childhood but at ages 20 (case 1) and 22 (case 6). The cases in which the disease started later than this could be explained by either trauma (case 13) or osteoarthritis (case 11).

In the preceding discussion the word "trophic" was in quotation marks because the foundation of this concept is still obscure. Clinical experience leaves little doubt that lesions of the nervous system cause disturbances in the normal development and nutrition of tissues in the supply area. Perforating ulcers and neurogenic arthropathy (Charcot joint) in tabes and ulcers in syringomyelia are striking examples of this kind of disorder, and several authors[23] have described other manifestations which had to be interpreted as trophic disturbances. However, the study of nervous influence on tissue nutrition has not elucidated the intimate nature of this influence. Whether there is a special system of trophic fibers or whether trophic impulses are efferent ("antidromic") impulses traveling in posterior root fibers, and whether the nerve effect on tissues is direct or secondary through the effect of nervous impulses on blood vessels, has not been definitely established.

There is a remarkable similarity between single features reported to be trophic in diseases of the nervous system and features of scleroderma. In both instances, the epidermis may be thin, smooth, shiny and devoid of wrinkles or it may exhibit hyperkeratosis, scaling and wrinkling. There is usually loss of elasticity. Changes in color due to either hyperpigmentation or depigmentation are frequent. Anhidrosis is more frequent, but hyperhidrosis sometimes occurs. I have seen a patient with a single patch of morphea whose initial complaint was localized hyperhidrosis in the area, but when the cutaneous changes developed more fully there was decreased sweating in this area. Both cyanosis and hyperemia have been described, and visible prominence of veins has been noted. Ulceration of the skin is likely to occur where it is subjected to continued pressure.

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23. Livingston, W. K.: Pain Mechanisms: A Physiologic Interpretation of Causalgia and Its Related States, New York, The Macmillan Company, 1943, p. 103. Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries, New York, Paul B. Hoeber, Inc., 1933 ed. 1, pp. 155 and 156. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940, p. 646. Wilson, S. A. K.: Neurology, edited by J. N. Bruce, Baltimore, Williams & Wilkins Company, 1940, vol. 2, p. 1400.

The deeper structures, too, are involved. The subcutaneous tissue may undergo hypertrophy followed by atrophy and feels hard and inelastic. In some cases the skin is thrown into folds. Because of muscle atrophy there may be decreased volume of the extremity, and the muscles may undergo fibrous changes with consequent decreased mobility, thus contributing to contracture deformities. All these features have been noted in 1 or more of the patients described in this paper, as well as in patients with trophic disturbances following frank lesions of the nervous system.

This clinical resemblance, together with the fact that spina bifida occulta and other abnormalities of the spine seem to be extremely common in patients with linear scleroderma, indicates that the tissue changes in linear scleroderma originate in lesions of the nervous system. In the majority of cases the responsible lesion seems to be localized in the central nervous system or spinal roots and is caused by either developmental anomaly or osteoarthritis. Exceptionally, however, the disease may originate in peripheral nerve lesions following trauma.

It is remarkable that in cases 1, 2 and 3 the arrangement and shape of the lesion on the left thigh are prototypically identical. Because of individual variations of segmentary distribution, it is difficult to evaluate this observation. However, as previously mentioned, according to the diagrams in the works of Brain[5] and Ranson[6] this band corresponds to the boundary of the second and third lumbar zones and may possibly be an overlap area in some persons. This observation, together with the possible relation of the lesion in case 13 to an overlap area, somewhat suggests that overlap may play some role in the development of linear scleroderma. One may speculate that trophic disturbances in overlap areas are "irritative" in nature rather than due to functional deficiency of nervous impulses, for localization in overlap areas necessarily means summation of some disturbance, and summation is conceivable only in cases of "irritative" disturbances.

The possibilities for roentgenologic study of linear scleroderma have not been exhausted in this presentation. Willis[24] has shown that interruptions in continuity occur oftener in lateral portions of the neural arch than in the central portion. These lateral defects cannot be seen in anteroposterior and lateral views, as employed in this survey, but require special oblique views which might in some cases explain the unilateral localization of the scleroderma lesion on the side of the bony defect. Also, roentgenograms made after subdural injections of a shadow-casting substance may demonstrate the evidence of cord pressure and locate the point of compression when it is present in spina bifida occulta, thus

24. Willis, T. A.: Backache from Vertebral Anomaly, Surg., Gynec. & Obst. **38**:658 (April) 1924.

providing the possibility of surgical treatment and prevention of progression of the scleroderma.

OTHER FORMS OF SCLERODERMA

This study was restricted arbitrarily to linear scleroderma occurring on the trunk and extremities. A similar study of linear scleroderma of the head ("en coup de sabre") is being prepared with particular reference to its relation to facial hemiatrophy. Recently, Wartenberg,[25] in his study on facial hemiatrophy and scleroderma "en coup de sabre," concluded that the latter represents abortive progressive facial hemiatrophy and that both conditions can be interpreted as being due to degenerative processes in the nervous system. My data support this view.

Because of great similarity of the tissue changes in the different forms of scleroderma, the possibility must be considered that morphea and diffuse progressive scleroderma may also represent neurogenic trophic disturbances similar to linear scleroderma.

Concerning morphea, there were combinations of linear scleroderma and morphea in 4 of the patients presented here. In case 1, although most lesions of the trunk followed the long axis of spinal root zones, others did not, and the round lesions among them could be considered morphea. Observations in roentgenograms of the cervical and thoracic aspects of the spine in that case were normal. A similar situation with abdominal lesions was encountered in case 5. In case 7 the patient had many round lesions on the thigh typical of morphea on an extremity involved with linear scleroderma. In case 13 there were four round discrete lesions of morphea on a buttock in addition to the linear lesion on the midline of the back. Furthermore, a patient with scleroderma "en coup de sabre" had typical morphea of the trunk. These combinations strongly suggest identical pathogenesis of linear scleroderma and morphea. On the other hand, it should be pointed out that linear scleroderma is characterized by (1) relatively early onset, (2) frequent occurrence of spina bifida occulta and (3) atrophy involving deep structures. In cases of morphea only, these characteristics are absent. The average age of onset in 20 unselected cases of morphea seen in this department was 28.8 years. The atrophic process did not involve muscle and bone in any of them. Finally, in connection with this study, roentgenographic examination of the spine was done in 6 patients with morphea only. Five showed no abnormalities of the spine which could be related to morphea, and only 1 patient, 69 years of age, showed severe osteoarthritis with osteophyte formation.

Thus, the available data are insufficient to decide whether linear scleroderma and morphea are related conditions, but the possibility that morphea is also of trophoneurotic origin cannot be excluded.

25. Wartenberg, R.: Progressive Facial Hemiatrophy, Arch. Neurol. & Psychiat. **54**:75 (Aug.) 1945.

Even less is known of the relationship beween the circumscribed forms and diffuse progressive scleroderma. Some evidence for the neurogenic basis of the generalized form was furnished by Rake.[26]

SUMMARY AND CONCLUSIONS

The histories and diagrams of lesions of 13 patients with linear scleroderma revealed that in the majority of cases the lesions lay in the long axis of spinal root zones and less frequently followed the distribution of peripheral nerves.

Seventy per cent of the patients with scleroderma of the legs, lower part of the abdomen or buttocks had spina bifida occulta, and some had other abnormalities of the lower part of the spine in addition. One patient with lesions of the arm had localized cervical osteoarthritis, and 1 with a lesion on the midline of the back had localized changes of the lower thoracic and lumbar aspects of the spine following trauma. In 1 patient the lesion developed after an injury and followed the course of a peripheral nerve.

Spina bifida occulta is sometimes associated with other local pathologic conditions which affect the nervous system. In linear scleroderma, these conditions plus the normal differential rate of growth of the spinal cord and spinal canal could determine the usual early onset of lesions of the leg, which in this series was 3.7 years.

Scleroderma has many characteristics typical of trophic disturbances associated with frank lesions of the nervous system, and all forms of scleroderma show similar tissue changes. Four of the patients had both morphea and linear scleroderma, which suggests a common pathogenesis for these entities. However, the relation of the two diseases requires further study.

Roentgenographic studies following injection of radiopaque substance intradurally may furnish evidence indicating surgical treatment to prevent progression of linear scleroderma of the legs.

The spatial distribution of lesions, the high incidence of demonstrable lesions of the spine in patients with linear scleroderma and the similarity of these lesions to trophic disturbances suggest that this disease originates from lesions in the nervous system.

NOTE.—Since the completion of this manuscript the presentation of case 6 and its discussion have been published. (ARCH. DERMAT. & SYPH. **57**:447 [March] 1948). H. Haxthausen (*Acta dermat.-venereol.* **27**:352, 1947) reported transplantation experiments the results of which led to the conclusion that morphea is a disease of trophoneurotic origin.

Dr. Stephen Rothman gave suggestions in this work and in the preparation of the manuscript.

26. Rake, G.: On the Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212 (April) 1931.

EXTERNAL USE OF "CARBITOL SOLVENT," "CARBITOL" AND OTHER AGENTS

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"CARBITOL solvent" (monoethyl ether of diethylene glycol) is of interest in dermatology because it is an ingredient of many commercial cosmetic products and of certain formulas recommended for use on the skin. It is said to confer a "vanishing effect, which appears to be esteemed in these preparations. This effect suggests that "carbitol" may be absorbed from the skin. If so, its use might be injurious, especially to the kidneys, which are readily damaged by members of the ethylene series of glycols.

In fact, von Oettingen and Jirouch,[1] Laug, Calvery, Morris and Woodard,[2] Kesten, Mulinos and Pomerantz[3] and Hanzlik and his collaborators[4] have demonstrated renal and hepatic damage in various ani-

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Read before the Dermatologic Section of the California Medical Association, Los Angeles, May 3, 1947.

1. von Oettingen, W. R., and Jirouch, E. A.: The Pharmacology of Ethylene Glycol and Some of Its Derivatives in Relation to Their Chemical Constitution and Physical Chemical Properties, J. Pharmacol. & Exper. Therap. **42**:355, 1931.

2. Laug, E. P.: Calvery, H. O.; Morris, H. J., and Woodard, G.: The Toxicology of Some Glycols and Derivatives, J. Indust. Hyg. & Toxicol. **21**:173, 1939.

3. Kesten, H. D.; Mulinos, M. G., and Pomerantz, L.: Pathologic Effects of Certain Glycols and Related Compounds, Arch. Path. **27**:447 (March) 1939.

4. (*a*) Hanzlik, P. J.; Lawrence, W. S., and Laqueur, G. L.: Comparative Chronic Toxicity of Diethylene Glycol Monoethyl Ether (Carbitol) and Some Related Glycols: Results of Continued Drinking and Feeding, J. Indust. Hyg. & Toxicol. **29**:233, 1947. (*b*) Hanzlik, P. J.; Luduena, F. P.; Lawrence, W. S., and Hanzlik, H.: Acute Toxicity and General Systemic Actions of Diethylene Glycol Monoethyl Ether (Carbitol), ibid. **29**:190, 1947. (*c*) Hanzlik, P. J.; Lawrence, W. S.; Fellows, J. K.; Luduena, F. P., and Laqueur, G. L.: Epidermal Application of Diethylene Glycol Monoethyl Ether (Carbitol) and Some Other Glycols: Absorption, Toxicity and Visceral Damage, ibid. **29**:325, 1947. (*d*) Luduena, F. P.; Lawrence, W. S.; Fellows, J. K.; Clark, W. H., and Hanzlik, P. J.: Excretion and Fate of Diethylene Glycol Monoethyl Ether (Carbitol) After Epidermal and Other Methods of Administration, Arch. internat. de pharmacodyn. et de thérap. **75**:1, 1947.

mals following ingestion, injection and external application of "carbitol" and "carbitol solvent." Largely for this reason, these products have been prohibited for internal administration. In view of the extensive use of "carbitol"-containing products by the public, it is surprising to find only one clinical report[5] on the possible hazards in the use of these products on human skin.

My interest in "carbitol solvent," or "carbitol," was especially aroused when its topical application in small amounts was observed to produce fatalities in rabbits, with great regularity.[4] It was then being synthesized and delivered to cosmetics manufacturers on a large scale. The "carbitol" content ranged from 5 to 50 per cent in shampoos and shaving, cleansing, cold, vanishing and other creams used in unknown amounts by a considerable proportion of the population. Workers in several large industries were exposed to contact with this chemical. It obviously was not as immediately fatal in human beings as in animals, but it seemed important to investigate its possible local and systemic effects in human beings. The results obtained are briefly presented in this paper.

A short description of the products used is first in order, particularly as the terminology in the literature is somewhat confusing. Monoethyl ether of diethylene glycol is the chemical name for "carbitol," a practically pure compound containing not more than 0.2 per cent of ethylene glycol. The commercial grade is generally referred to as "carbitol solvent" or "technical carbitol" and is a mixture of 70 per cent "carbitol" and 30 per cent ethylene glycol. It has been widely used for years as a solvent or vehicle in dye, lacquer and cosmetic industries.[6] In cosmetics a content of not more than 5 per cent is permitted by the Food and Drug Act.

Since "carbitol" is more uniformly absorbed from the skin of animals than ethylene glycol[4] and since it is the principal component in "carbitol solvent," considerable interest is attached to it. Its properties are rather interesting.

"Carbitol" is a clear colorless liquid with a mild pleasant odor. It has a high boiling point (201.9 C.) and is only slightly hygroscopic. It definitely retards the drying of ointments. When dyes are incorporated, their intensity and spreading power are increased, giving the resulting preparation a more uniform color. It is also an excellent solvent for most perfumes. "Carbitol" is water soluble, and a mutual solvent for

5. Cranch, A. C.; Smyth, H. F., Jr., and Carpenter, C. P.: External Contact with Monoethyl Ether of Diethylene Glycol (Carbitol Solvent), Arch. Dermat. & Syph. **45**:533 (March) 1942.

6. Emulsions, ed. 7, New York, Carbide and Carbon Chemicals Corporation, 1946.

soaps, oils and waxes, correcting immiscibility and forming finer dispersions in water. It has a soothing softening effect on the skin and does not have the stickiness or slight burning sensation encountered with solvents containing glycerin. A similar emollient effect is noticeable in lotions after addition of 5 per cent "carbitol." It is difficult to incorporate more than 20 per cent "carbitol" in an ointment, and use of more than 5 per cent appears unnecessary. The results described first are those of patch tests in which certain glycols were used as controls for "carbitol solvent" and "carbitol."

TABLE 1.—*Results of Patch Tests with Undiluted "Carbitol Solvent" and Propylene Glycol*

Substance	Number of Patients	Positive Results	Negative Results
"Carbitol solvent"	99	24	75
Propylene glycol	99	17	82

PATCH TESTS WITH "CARBITOL SOLVENT," "CARBITOL" AND SOME GLYCOLS

Undiluted "carbitol solvent" and propylene glycol patch tests were applied to 99 patients in the Stanford Skin Clinic. Muslin squares were saturated with the test solution, covered with a larger piece of "cellophane" and then secured with elastic adhesive or "scotch" tape. They

TABLE 2.—*Results of Patch Tests with Undiluted "Carbitol Solvent" and Propylene Glycol Repeated Four Weeks After the Initial Test**

	Positive	Negative	Positive	Negative
"Carbitol solvent"	9	4	6	26
Propylene glycol	7	6	4	28

*In the initial patch test, results were positive in 13 persons (1 of whom had a negative reaction to propylene glycol) and negative in 32.

were removed after forty-eight hours and the sites inspected again at ninety-six hours and weekly thereafter for one month.

The results obtained with "carbitol solvent" and propylene glycol in 45 patients, who returned for repeat patch tests four weeks later, are given in table 2.

The result was not entirely in agreement with the previous response in each person, but this probably only reflects the difficulty encountered

in deciding whether or not a reaction was positive. No strongly positive reactions were seen, suggesting, in this small group, that the sensitizing powers of "carbitol solvent" and propylene glycol are not great.

Patch tests were then done on 31 additional patients, using aqueous dilutions of "carbitol," "carbitol solvent" and several glycols, as indicated in table 3. All of the positive reactions in tables 1, 2 and 3 consisted merely of faint erythema, restricted to the area tested and persisting at least forty-eight hours after removal of the patch. Persistent erythema was also noted in rabbits after epidermal applications, and cutaneous sections showed a mild lymphocytic infiltration of the corium.[4] Apparently, this erythem represents a mild irritant effect, rather than sensitization, and is not specific, since it occurred with all agents, regardless of chemical composition. There were no positive reactions to 5 per cent concentrations of any of the substances tested, and to the 10 per cent group

TABLE 3.—*Positive Reactions to Patch Tests with "Carbitol" and Some Glycols in 31 Additional Patients*

	No. of Patients with Positive Reactions to the Concentrations Used				
	100 Per Cent Concentrations*	50 Per Cent Concentrations*	25 Per Cent Concentrations*	10 Per Cent Concentrations*	5 Per Cent Concentrations*
"Carbitol solvent"	14	11	2	1	0
Ethlene glycol	12	8	5	1	0
Propylene glycol	11	9	1	0	0
Diethylene glycol	4	2	1	0	0
"Carbitol"	5	3	1	0	0

*Aqueous.

only one reaction to "carbitol solvent" and one to ethylene glycol occurred. Perhaps the true incidence of reactions to patch tests is indicated by the residual scaling seen in thirteen undiluted "carbitol solvent," and ten propylene glycol, sites and the hyperpigmentation which occurred in 3 patients of each of these groups.

The age, sex, race, type of skin, complexion, history of cutaneous sensitivity, atopy and diagnostic factors were unimportant in the incidence of reactions. In no instance was a strongly positive reaction to a patch test seen in dermatitis due to cosmetic contact.

These results with "carbitol solvent" differ somewhat from those of Cranch, Smyth and Carpenter,[5] who reported "definite reactions" to "carbitol solvent" in only 7 of 98 patients. Their wording suggests that they encountered additional indefinite reactions. In their series, the initial period of contact was seven days, and after a ten day interval the same areas were retested for three days. Sixty persons gently rubbed the

"carbitol solvent" on one wrist and glycerin on the other for five minutes on ten consecutive days, leaving the areas unwashed for one hour. Seven patients had positive reactions, consisting of mild dermatitis of the entire area. Most patients reported transient congestion from both materials, so that the mild irritation was not specific for "carbitol solvent." Cranch, Smyth and Carpenter also compared the irritant effects of "carbitol solvent" and glycerin on the rabbit conjunctiva and observed them to be slight. These materials, in 50 per cent and 70 per cent concentrations, were applied to rabbit wounds of different sizes and depths, without demonstrable delay in healing or injury from absorption.

Maynard[7] tested 225 patients with undiluted "carbitol solvent," "carbitol" and dilutions in "carbowax" and ethyl alcohol. Using adequate controls, he observed only four mildly positive reactions in the entire group.

GENERAL EFFECTS FROM EXTERNAL APPLICATIONS OF "CARBITOL SOLVENT" AND "CARBITOL" IN DERMATOLOGIC FORMULAS

One formula containing "carbitol" (polyethylene glycol) was found in the dermatologic literature. Reuter[8] advised prophylactic application of a vanishing cream containing 9 per cent "carbitol" for the protection of hosiery workers who handled silk soaked in a highly alkaline solution. This preparation was also recommended by Anderson[9] in two noteworthy contributions to clarity in diagnosis and treatment of industrial dermatoses.

"Carbitol solvent" was used in 55 ambulatory patients and "carbitol" in 9. Mixtures of from 5 per cent to 50 per cent "carbitol solvent" were prescribed in water, calamine lotion N. F., compound starch lotion, rose water ointment U. S. P. and a proprietary product containing cholesterolized wool fat base.[10] The diagnosis and the person largely determined the vehicle employed, as well as the extent, frequency and total period of application. Routine instructions were to apply the medicament to the entire body, or to the affected parts, three or more times daily. The duration of treatment ranged from one to twelve weeks. Twenty-six patients, or 40 per cent, were treated for contact dermatitis,

7. Maynard, M. T. R.: Personal communication to the author.

8. Reuter, M. J.: Prevention of Industrial Dermatitis, Indust. Med. **10**:147, 1941.

9. Anderson, N. P.: Contact Dermatitis with Special Reference to Industrial Dermatitis, Indust. Med. **12**:584, 1943; New Concepts in the Therapy of Industrial Contact Dermatitis, California & West. Med. **62**:17,1945.

10. The trade name of this product is "aquaphor," and it is said to contain "complex high molecular hydroxyl animal fat compounds readily binding water incorporated in indifferent aliphatic hydrocarbons and absorbing at least three times its own weight of water or aqueous solutions of medicaments."

with the diseases in the balance of the patients fairly evenly distributed among other common dermatoses. The vehicle, average weeks of use and estimated amount of "carbitol solvent" applied, for the entire group, are shown in table 4. The same formulas containing "carbitol" had been used in rabbits by Hanzlik and his co-workers[4] and did not appear to hinder absorption of the "carbitol," since there was a rate of mortality of 50 per cent in these animals following thirty daily applications of 0.32 cc. per kilogram of body weight, equivalent to a total of 156.8 cc. per week in a human being of 70 Kg. The average survival period was twenty-six days.

The largest total amount of "carbitol solvent" applied by any patient was 648 cc. This was used over a period of nine weeks, averaging 72 cc. per week. The largest weekly application was 180 cc. for two weeks.

TABLE 4.—*Topical Use of "Carbitol Solvent" in Different Vehicles*

Number of Patients	Vehicle	Period of Application (Weeks)	"Carbitol Solvent" (Cc. per Week)
5	Water	6.2	52.0
5	Calamine lotion N.F.	2.8	16.0
28	Compound starch lotion*	3.2	33.0
5	Cold cream U.S.P.	1.6	23.0
21	"Aquaphor"[10]	2.3	27.0

*The composition of compound starch lotion was as follows: zinc oxide, 10 per cent; starch, 10 per cent; glycerin, 1 per cent; and lime water, enough to make 100 per cent.

Repeated questioning and examination revealed no symptoms or signs of toxicity in any of the 64 patients. Three mild exacerbations of the presenting dermatosis occurred and may have been due to "carbitol solvent," although this was not proved. Urinalysis, complete blood cell count and blood urea, phenosulfonphthalein and cephalin-cholesterol flocculation tests were done before, and at various intervals after, the application of "carbitol solvent" in one third of the patients, and some of these tests were done in a number of others, but no injurious effects were demonstrable by these methods.

EXCRETION OF MONOETHYL ETHER OF DIETHYLENE GLYCOL AND GLUCURONIC ACID

The urinary excretion of monoethyl ether of diethylene glycol was determined in twenty-four hour specimens of urine from 9 patients, according to a distillation method developed by Luduena and his co-workers[4] and by direct titration for oxidizable material in urinary fil-

trates.[11] Table 5 shows the total and weekly amounts of "carbitol solvent" and "carbitol" applied, which were fairly representative of the entire group. No definite excretion was observed, nor was diethylene glycol monoethyl ether xanthate demonstrable in thirteen specimens of urine from 3 patients. Deichmann's method was utilized for estimating the

TABLE 5.—*Urinary Excretion of Monoethyl Ether of Diethylene Glycol and Glucuronic Acid After External Application of "Carbitol Solvent" and "Carbitol"*

Patient	Sex	Total "Carbitol" Applied (Cc.)	Period of Application (Weeks)	"Carbitol" (Cc. per Week)	Vehicle	Number of 24 Hour Specimens of Urine Examined for			
						DEGM* by Distillation†	Glucuronic Acid	DEGM* Xanthate	Follow-up (Mo.)
Tr.	♂	510 120	12 8	42.5 15.0	Water Water	4 5	2 —	— 5	— 24
Dy	♂	345‡	12	29.0	Water and "aquaphor"[10]	4	4	4	16
Co.	♀	180	2	90.0	Compound starch lotion	1	1	—	5
Sn	♂	60‡	2	30.0	"Aquaphor"	1	1	—	12
Bn	♂	48	3	16.0	"Aquaphor"	4	4	4	45
Yg	♀	48‡	4	12.0	"Aquaphor"	1	1	—	12
As	♂	12‡	2	6.0	"Aquaphor"	1	3	—	2

*DEGM is monoethyl ether of diethylene glycol.

†Three specimens of urine from 2 other patients not in the table were examined, with negative results; the total was twenty-four specimens of urine.

‡These patients received mixtures containing "carbitol," all others receiving mixtures containing "carbitol solvent."

level of urinary glucuronic acid, a conjugate of diethylene glycol monoethyl ether, with negative results in sixteen specimens of urine from 7 patients. These negative results for glucuronic acid complemented those for monoethyl ether of diethylene glycol in human specimens of urine and, in turn, agreed with the essentially negative results in rabbits.[12]

SUMMARY AND CONCLUSIONS

Patch tests indicate that monoethyl ether of diethylene glycol does not possess high sensitizing powers for human skin and is probably seldom responsible for contact dermatitis from cosmetics.

11. The determinations of the monethyl ether of diethylene glycol and glucuronic acid and isolation of the xanthate were made by Dr. F. P. Luduena and Miss Jean K. Fellows of the Stanford Department of Pharmacology and Therapeutics.

12. Fellows, J. K.; Luduena, F. P., and Hanzlik, P. J.: Glucuronic Acid Excretion After Diethylene Glycol Monoethyl Ether (Carbitol) and Some Other Glycols, J. Pharmacol. & Exper. Therap. **89**:210, 1947.

"Carbitol solvent" and "carbitol" appear innocuous when applied externally in lotions and ointments, even in rather high concentrations used over a considerable period of time.

Absorption in human beings is not demonstrable, and is apparently negligible, when "carbitol solvent" or "carbitol" is applied in amounts greater than would be reasonably expected in the routine application of cosmetics.

It is believed that the addition of "carbitol" to certain prescriptions for lotions and ointments will improve them by making them more uniform in consistency, by retarding drying and by enhancing their emollient effect.

TINEA CAPITIS

Due to Combined Infection With Microsporum Audouini and Microsporum Lanosum; Report of a Case

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COMBINED infections with fungi of various types are rarely reported. Muskatblit[1] in 1941 reviewed 36 cases in the literature and put on record 6 cases of his own, the patients having been observed during a period of ten years. He[2] added another case to this list in 1946. Lewis and Hopper[3] in 1943 presented the histories and critical evaluation of 23 cases of combined, consecutive and concurrent fungous infections[4] among 1,200 persons suspected of having a fungous disease. Sabouraud[5] observed an undetermined number of combined infections of the scalp with Trichophyton crateriforme and a microsporum.

With the exception of Sabouraud's observations, the aforementioned 66 cases include involvement of one or several sites of the human skin and its appendages with two or more different fungi. The scalp was the site of a combined infection in only 19 of these 66 cases (table 1). Eight different fungous associations occurred on the scalp (table 2). Lombardo did not mention the specific trichophyta isolated in his cases of combined favus and trichophytosis. The assignment of this group to one of the other

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1. Muskatblit, E.: Combined Fungous Infections: Report of Six Cases with a Review of Thirty-Six Cases from the Literature, Arch. Dermat. & Syph. **44**:631 (Oct.) 1941.

2. Muskatblit, E.: Dermatophytosis Due to Combined Infection with Trichophyton Interdigitale and Trichophyton Purpureum: Report of a Case, Arch. Dermat. & Syph. **54**:558 (Nov.) 1946.

3. Lewis, G. M., and Hopper, M. E.: Concurrent, Combined and Consecutive Fungous Infections of the Skin: Cultural Experiences, Arch. Dermat. & Syph. **47**:27 (Jan.) 1943.

4. Lewis and Hopper used the term "consecutive" in instances of fungous infection due to one pathogen followed by a second fungous infection due to a species different from the first. "Concurrent" denoted infection with two or more different organisms, at different sites, without causative relation. The term "combined" was reserved for infections with two or more fungi isolated from the same site.

5. Sabouraud, R.: Les teignes, Paris, Masson & Cie, 1910.

TABLE 1.—*Combined Fungous Infection of the Scalp, Reported in the Literature*

Author (Date)	Number of Cases	Causative Fungi	Comment
Aubert (Lyon. méd. 22:583, 1876)	2*	T. violaceum and T. schoenleini	
Bodin (Ann. de dermat. et syph. 1:327, 1910)	1*	T. violaceum and T. schoenleini	
Barbaglia (Gior. ital. di mal. ven. 49:911, 1914)	1	T. violaceum and T. cerebriforme	
Brault and Viguier (Ann. de dermat. et syph. 6:169, 1916)	1	T. violaceum and T. schoenleini	
Finkelstein and Sigalova (Samprosvet Guvzdrava, 1925)	1	T. violaceum and M. sp.†	*
Lombardo (Gior. ital. di dermat. e sif. 67:258, 1926)	3	T. sp.† and T. schoenleini	* Mentioned
Karrenberg (Arch. Dermat. & Syph. 17:519 [April] 1928)	1	E. inguinale and T. purpureum‡	*Described as E. rubrum-like fungus
Karrenberg (Arch. f. Dermat. u Syph. 154:668, 1928)	1	T. niveum§ and T. cerebriforme	
Tschernogubow and Muskatblit (Arch. f. Dermat. u Syph. 159:46, 1929)	3	T. violaceum and T. schoenleini	
Tschernogubow and Muskatblit (Arch. f. Dermat. u Syph. 159:46, 1929)	3	T. crateriforme and T. schoenleini	
Tschernogubow and Muskatblit[14] (Arch. f. Dermat. u Syph. 159:46, 1929)	1	M. lanosum and T. schoenleini	
Muskatblit[1] (1941)	1	T. violaceum and T. schoenleini	

*No culture methods employed.
†Species not identified.
‡Described as Epidermophyton-rubrum-like fungus.
§Described as Trichophyton niveum denticulatum.

TABLE 2.—*Reports in the Literature of Fungous Combinations and Their Relative Frequency of Occurrence*

Fungous Combinations	Number of Cases
T. violaceum and T. schoenleini	8*
T. sp.† and T. schoenleini	3
T. crateriforme and T. schoenleini	3
T. violaceum and M. sp.†	1
T. violaceum and T. cerebriforme	1
M. lanosum and T. schoenleini	1
T. niveum‡ and T. cerebriforme	1
E. inguinale and T. purpureum§	1

*Included are 3 cases in which no cultural methods were employed.
†The clinical features warrant this inclusion. Species was not mentioned.
‡Reported as Trichophyton niveum denticulatum.
§Reported as Epidermophyton-rubrum-like fungus.

"favus-trichophytosis" combinations would reduce the number of fungous associations observed on the scalp to seven. The most frequent was the joint occurrence of Trichophyton violaceum and Trichophyton schoenleini (eight times). The combination of T. crateriforme and T. schoenleini was reported three times. Each one of the following combinations is on record: T. schoenleini and Microsporum lanosum, T. violaceum and Trichophyton cerebriforme, Epidermophyton floccosum and Trichophyton purpureum, Trichophyton niveum and T. cerebriforme and T. violaceum and Microsporum "sp." (species not reported).

Microspora were listed only twice; once in combination with T. schoenleini and once with T. violaceum. The miscosporum occurring in conjunction with T. violaceum was not identified; the other was M. lanosum.

This paper presents the history and critical evaluation of the first recorded case of a scalp infected with both Microsporum audouini and M. lanosum.

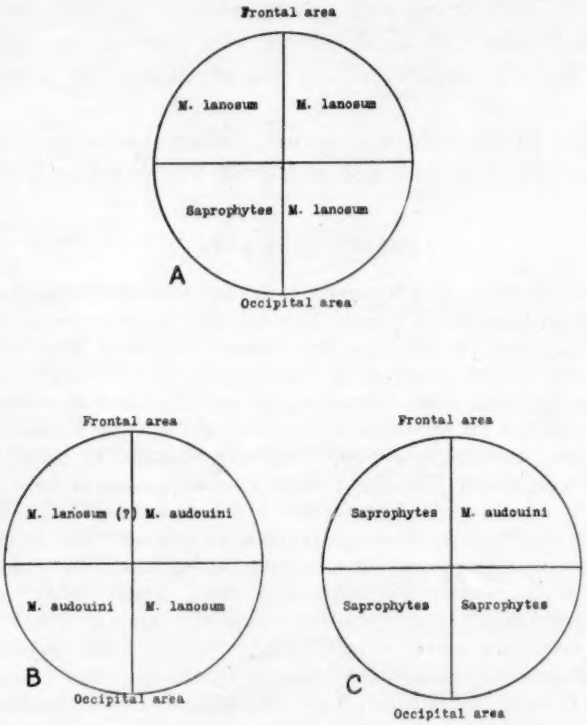
REPORT OF A CASE

On March 14, 1946, an 11 year old Negro girl was referred to the outpatient department of the Long Island College Hospital with the diagnosis of tinea capitis. M. audouini had been identified as the causative fungus in January 1945. The patient had been treated unsuccessfully with various salves and tincture of iodine for fifteen months, both prior and subsequent to epilation with roentgen rays in January. Examination on admission to the clinic of the Long Island College Hospital showed small spots of "gray patch" ringworm scattered on the scalp. Signs of inflammation were absent. The gray patches disclosed groups of bright fluorescent hairs under filtered ultraviolet rays. Culture of fluorescent hairs yielded M. audouini, confirming the observations of the previous investigator. This initial examination was followed by eleven months' treatment, during which the fungicidal agents employed failed to produce any substantial effect. These agents included ammoniated mercury ointment, compound ointment of benzoic acid, sulfur ointment, a compound containing iodine, thymol, camphor and oil of eucalyptus in olive oil, "desenex" ointment (contains 5 per cent undecylenic acid and 20 per cent zinc undecylenate in an ointment base), 5 per cent salicylanilide in "carbowax" (polyethylene gylcol) and cetyltrimethylammonium pentachlorophenate, together with manual epilation. The patient attended the clinic at weekly intervals. On Feb. 20, 1947, the mycologic examination of fluorescent hairs of the scalp was repeated. The culture yielded M. lanosum. Repetition of the tests on March 4 and March 18 showed M. audouini on the former and M. lanosum on the latter date.

Because of these apparently contradictory results of the laboratory studies, cultures were taken separately, on April 1, from the left and right frontoparietal areas and from the right and left occipital areas. The right and left frontoparietal as well as the right occipital area yielded M. lanosum. The culture of the left occipital area was overgrown with saprophytic fungi and bacteria; pathogenic dermatophytes were not obtained from that area (*A* of the figure). On April 15, cultural examination of the four areas was repeated. M. lanosum was identified in the right occipital area and M. audouini in the left occipital and right frontoparietal region. The tube containing the inoculum from the left frontoparietal area was accidentally broken before microscopic examination of culture material could be

performed. The rate of growth and the color of the colony, however, were indicative of M. lanosum (*B* of the figure). On May 27, cultures from the aforementioned four areas of the scalp yielded M. audouini only in the right frontoparietal region; the tubes from the other areas were overgrown by saprophytes (*C* of the figure).

It is noteworthy that the clinical character of the infection remained invariably and uniformly that of "gray patchy" ringworm, without signs of inflammation. During the period of repeated mycologic studies, the topical applications of therapeutic agents was continued, except on the days of and preceding the visits to the clinic. The patient had menstruated, at irregular intervals, since the beginning of



Diagrams showing cultural results in each area. *A*, results of cultures on April, 1, 1947. *B*, results on April 15. *C*, results on May 27.

1946. The blood cell count in March 1946 revealed a moderate degree of anemia, with 3,590,000 red blood cells and 10.5 Gm. of hemoglobin. The white cell count was 5,950, with 50 per cent neutrophils, 44 per cent small lymphocytes and 6 per cent eosinophils. No abnormal red or white blood cells were seen. The cholesterol content of the blood was 210 mg. per hundred cubic centimeters.

METHOD AND DIAGNOSTIC CRITERIA

The mycologic diagnosis was based on accepted technics and criteria. Infected hairs, identified by filtered ultraviolet rays, were placed on Sabouraud dextrose agar slants (Difco). Each slant was inoculated with

ten hairs. The tubes were kept at room temperature and observed for signs of fungous growth for at least three weeks, at intervals of from two to seven days. When a fungous colony had reached a diameter of about 2 cm., material from its center was taken for microscopic examination and subcultures were performed on three other dextrose agar slants. The latter were kept under macroscopic and microscopic observation for a period of at least six weeks.

M. lanosum developed quickly and grew relatively rapidly; it covered the entire surface of the agar slant in an average period of from seven to fourteen days. The aerial mycelium was relatively abundant. In younger colonies a yellow lemon-colored pigment appeared, particularly conspicuous when viewed with transmitted light. As the colony aged, its color changed from yellow to brownish red. At a still later stage of development, the surface, principally at the center of the colony, became powdery.

M. audouini started to grow later, and its rate of development was slower than that of M. lanosum. It took from two to four weeks to cover the entire surface of the agar slant. The aerial mycelium was closely matted and relatively scanty. There was no yellow lemon-colored pigment present; instead, a brownish red pigment appeared relatively early on the under surface of the colony.

The color of the growth could be relied on as a differential diagnostic criterion only in the early stages of the cultures. With increasing age a diffuse brownish red pigment pervaded the colonies, which made the difference in pigmentation an unsafe diagnostic criterion.

Exact diagnosis of the nature of the colony was made by microscopic examination of culture mounts. The characteristic feature of M. lanosum was the large amount of macroconidia of the tapering fuseaux type, with four to seven compartments. These were seen on mounted slides as early as five days after transplantation and remained demonstrable as late as one hundred and forty-four days. Fuseaux of this type were practically absent in culture mounts of M. audouini.

COMMENT

The facts of special interest in this case are as follows:

In a Negro girl, near sexual maturity, ringworm of the scalp developed which was extremely resistant to treatment for at least two and

one-half years. At an earlier stage of the infection M. audouini was seen by two observers, with an interval of about one year between each examination. Eleven months after the initial examination at the clinic of the Long Island College Hospital (presumably more than two years after onset of the symptoms), a mycologic study revealed the presence of M. lanosum as well as M. audouini. Thereafter both fungi were demonstrated repeatedly. Although both fungi were never grown together on the same agar slant, they were demonstrated simultaneously and consecutively at close proximity; e.g., on April 15, 1947, M. lanosum was isolated from two areas of the scalp and M. audouini from two others. Furthermore, on April 15 and May 27, M. audouini was identified in an area from which M. lanosum had been isolated on April 1.

A comparison of *A* and *C* of the figure suggests the possibility that the combined infection might have been localized in the right frontoparietal area. At this site M. lanosum and M. audouini were identified alternately, while in the other three areas the serial tests revealed either the identical dermatophyte or a saprophyte.

The two different fungi could not be correlated with two different types of lesions of the scalp. Uniformly, there was lack of inflammatory response. As a matter of fact, at a later stage of the infection, only filtered ultraviolet rays disclosed the presence of affected hairs. This mild clinical course, characteristic of the majority of the anthropophilic infections, prevailed throughout the period of observation.

Although no conclusive evidence can be adduced, it is likely that the M. audouini infection antedated the combined infection of the scalp. This statement is based on the facts that two observers saw only M. audouini within one year and the clinical appearance was that commonly seen in M. audouini infections. At some later date a superimposed infection with M. lanosum may have taken place. It is noteworthy that the character of the disease did not change and no inflammatory response occurred.

The question as to whether the close association of the two fungi was instrumental in this unusual resistance to all therapeutic agents used cannot be decided at this juncture. It appears to be linked up with another problem, namely, whether combined infections are in reality as rare as the sparse reports of the literature seem to indicate. Practically all cases of combined fungous infections reported came to light rather by

accident than by deliberate search. It seems possible that a systematic approach by repeated laboratory studies at intervals would uncover more cases. In this manner, light might be thrown on a possible causal relation between resistance to treatment and double infection.

SUMMARY

A case of tinea capitis is reported in which both Microsporum audouini and Microsporum lanosum were present. The clinical appearance was at all times and in all sites that commonly seen in the anthropophilic type of the disease. There was no response to the therapeutic agents employed.

It is suggested that material for examination in cases of suspected or proved fungous infection of the scalp be taken from several diseased sites and that such examinations be repeated at relatively frequent intervals.

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TREATMENT OF EARLY SYPHILIS WITH PENICILLIN IN OIL AND WAX

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THE TREATMENT of syphilis with penicillin as an office procedure is highly desirable, since, for social or financial reasons, many patients wish to avoid hospitalization. The delayed absorption of penicillin in peanut oil and wax permits the use of this preparation on an ambulatory basis, and several reports have appeared in which this form of treatment has been shown to be satisfactory in the treatment of early syphilis.[1]

During the past year I have used penicillin in oil and wax alone in the treatment of 78 patients with primary and secondary syphilis. This report presents the results obtained and the untoward reactions that I observed in this group of patients.

MATERIAL AND PROCEDURE

From February 1946 to August, 78 patients with early syphilis were treated with penicillin in oil and wax. Three of these patients failed to return for follow-up observation and are not included in this report. Of the remaining 75 patients, there were 35 male and 40 female patients; 6 were white, and 69 were Negro. The diagnoses at the onset of treatment were: primary syphilis in 14 patients, secondary syphilis in 44 patients and recurrent secondary syphilis in 17 patients.

The diagnosis of early syphilis was confirmed in 41 patients by the demonstration of Treponema pallidum in the lesions. In 31 cases the diagnosis was based on typical cutaneous lesions of secondary syphilis, associated with strongly positive serologic reactions. The remaining 3 patients showed no cutaneous lesions, but had other manifestations of early syphilis, such as decided generalized lymphadenopathy, iritis and a rising serologic titer.

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1. (*a*) Romansky, M. J., and Rein, C. R.: Treatment of Early Syphilis with Calcium Penicillin-Oil-Beeswax, J. A. M. A. **132**:847 (Dec. 7) 1946. (*b*) Thomas, E. W.; Landy, S., and Cooper, C.: Rapid Treatment of Early Syphilis with Penicillin in Beeswax and Oil, J. Ven. Dis. Inform. **28**:19, 1947. (*c*) Koch, R. A.: Ambulatory Intensive Treatment of Syphilis with Calcium Penicillin in Oil and Wax, Urol. & Cutan. Rev. **50**:461, 1946.

Only 2 patients had negative reactions to serologic tests for syphilis; both of these had primary lesions with positive results on dark field examination. The patients in whom the disease was diagnosed as recurrent secondary syphilis were patients in whom evidence of secondary syphilis had developed following previous treatment with aqueous solution of penicillin or arsenic and bismuth compounds.

A quantitative Kahn test of the blood and a spinal fluid examination were performed for every patient before treatment was started. Cell counts of the spinal fluid were done in the Fuchs-Rosenthal chamber within an hour after the spinal fluid was taken. Total protein determinations in the spinal fluid were made by electrophotometric measurement of the turbidity produced by the addition of sodium sulfosalicylate to the spinal fluid. The electrophotometer had been standardized with serum, the total protein of which had been determind by the Kjeldahl method. Colloidal tests were done with mastic solution. The Kolmer complement fixation tests was done with serial dilutions of spinal fluid from 0.5 cc. to 0.0312 cc.

Four patients had positive Wassermann reactions of the spinal fluid, 2 of whom also had an increase in the spinal fluid cell count and protein. One of these 4 patients showed unilateral facial paralysis and evidence of meningitis due to syhilis.

Two ambulatory treatment schedules were employed, each consisting of a total dose of 9,600,000 units of pencillin in wax and oil. One group of 52 patients was given daily injections of 600,000 units for sixteen days. The second group, consisting of 23 patients, received an injection of 600,000 units twice a week for eight weeks. The schedule selected for each patient depended chiefly on the convenience of the patient and not on the severity or type of illness. All patients were instructed to return at monthly intervals for repeated serologic tests. Although no further treatment was advised following the completion of treatment with penicillin in oil and wax, 3 patients received a few additional injections with arsenic compound or penicillin from their private physicians for either pregnancy or a persistently positive serologic reaction. Seventeen patients were observed for six to nine months, 17 for ten to twelve months and 34 for thirteen to nineteen months. Seven patients had a relapse within six months after treatment and were given another form of treatment.,

RESULTS

The table shows the results of the penicillin therapy in the 75 patients. Fifty-two of the patients (69.3) per cent) attained a negative reaction to the serologic test for syphilis, which was maintained throughout the period of observation. The length of time required to attain a negative reaction varied considerably. Although negative serologic reactions were attained in a few patients by the third month, four to seven months were usually necessary. Occasionally as long as twelve to fifteen months were required before the serologic reaction became negative.

Only 8 patients in this series continued to show a positive reaction to the serologic test for syphilis. The Kahn titer in each of these 8 patients was steadily decreasing, and, at the time of writing, the titer in all but 1 was less than 4 Kahn units. This patient continued to have a positive reaction, with 20 Kahn units, after one year of treatment for recurrent secondary syphilis. Follow-up observation in these 8 cases must be

continued, however, to determine their ultimate serologic and clinical outcome.

In 15 (20 per cent) of the 75 patients in this study treatment was considered to have failed, and these patients showed serologic or clinical evidence of an active infection following treatment with penicillin in oil and wax. In 9 of the 15 recurrent cutaneous lesions of early syphilis developed, while 5 others showed a rising serologic titer without lesions. In the remaining patient treatment was considered to have failed because no change had occurred in the spinal fluid cell count after four months of treatment with penicillin in oil and wax for recurrent secondary syphilis with meningitis due to syphilis.

In 4 (23.4 per cent) of the 17 patients in whom the disease had been diagnosed as recurrent syphilis prior to treatment, evidence of an active syphilitic process again developed following the penicillin therapy. This is somewhat higher than the number of patients with relapse (18.9 per cent) among the patients treated for the first time.

The relative efficacy of the two treatment schedules employed in this study is of interest. Failure of treatment occurred in 11 (21.1 per cent) among the 52 patients treated with daily injections, whereas failure occurred in 4 (17.1 per cent) among the 23 patients treated twice a week. While the number of patients in each of these groups is rather small and definite conclusions cannot be made, it appears, nevertheless, that the results obtained with injections of penicillin in oil and wax two times a week were at least as good as those obtained with daily injection.

At least 2 of the 15 patients in whom treatment was classified as having failed in this study appeared to have reinfections rather than relapsing infections. One of these patients was a Negro who had been treated for seronegative primary syphilis. Six months following treatment he returned with another seronegative primary lesion at a site different from that of the initial chancre. His wife had been treated in this clinic for secondary syphilis and had presented recurrent secondary manifestations several weeks prior to the time of the appearance of her husband's lesion. The second patient, a Negro, had attained a negative reaction to the serologic test for syphilis three months after treatment for secondary syphilis. He returned five months after treatment, however, with a primary lesion and a doubtful reaction to the serologic test. When first treated with penicillin in oil and wax, he had given the name of the only person whom he had contacted, who was referred to another clinic for treatment. It was not until the patient returned with another lesion that it was learned that the person whom he had contacted had never received treatment and had, in the meantime, married the patient. Two other patients with recurrent syphilis also presented what appeared clini-

cally to be reinfection rather than relapse, but this, of course, could not be proved.[2]

Examinations of spinal fluid were repeated in all cases of relapse and for the 4 patients who had had positive reactions of the spinal fluid before treatment. In none of the patients with initially negative reactions of the spinal fluid and subsequent clinical or serologic relapse did there develop a positive reaction of the spinal fluid. Three of the patients with initially positive reactions of the spinal fluid had a satisfactory serologic response, and the spinal fluid in these patients became normal. The remaining patient, as mentioned in a foregoing paragraph, showed no reduction in spinal fluid cell count four months following treatment with penicillin in oil and wax for recurrent secondary syphilis with meningitis due to syphilis.

REACTIONS

The reactions encountered with the penicillin therapy were generally minor and consisted chiefly of pain and tenderness at the site of injection. In a few patients local pain and tenderness became rather severe after the eighth to the tenth injection, and considerable encouragement was necessary before these patients consented to continue treatment.

Leukocyte counts and differential examinations of blood smears were done for 28 patients. Fourteen of these showed definite eosinophilia, the percentages of eosinophils ranging from 6 per cent to 35 per cent. In 5 patients urticaria developed, which responded promptly to treatment with diphenhydramine hydrochloride ("benadryl hydrochloride").

Herxheimer reactions were encountered in a few patients. Since all the patients in this study were ambulatory, only the severe reactions were noted and probably many of the milder ones were unobserved. In the majority of instances, the reactions consisted of fever, chilly sensations, headache and temporary exacerbation of symptoms.

Although the mucosal and cutaneous lesions usually disappeared rather rapidly with treatment with pencillin in oil and wax, I observed 2 patients in whom papular secondary lesions continued to develop during the first seven to ten daily injections of the penicillin mixture. Some of the older lesions in these patients showed signs of involution and healing, but fresh lesions continued to appear. Results of dark field examinations were negative for these 2 patients when examinations were repeated during the first week of treatment. The number of papules had increased to such an extent during the first week of treatment that change of treatment was contemplated. Histologic examination of the papules revealed

2. Moore, J. E.: The Changing Concept of Reinfection with Syphilis and Its Applicability as a Criterion of Cure, editorial, Am. J. Syph., Gonor. & Ven. Dis. **29**:474, 1945.

an acute reaction in addition to the syphilitic process. The detailed histologic observations for these 2 patients will be reported elsewhere.[3] Although papular secondary syphilides are known to heal slowly, I have never observed this phenomenon with arsenical therapy. I believe that these patients may have had an unusual form of Herxheimer reaction, manifested by a prolonged exacerbation of cutaneous lesions.

In 1 patient pulmonary emboli developed following the intramuscular injection of penicillin in oil and wax. This patient had a severe attack of coughing while still on the treatment table and complained of tasting the medication. Several days later fever and severe dyspnea developed, and the patient was hospitalized. Roentgenographic examination of the chest revealed multiple areas of pulmonary consolidation. The patient was extremely ill for several days, but eventually recovered with symptomatic therapy. This case has been reported in detail elsewhere.[4] I have since observed 1 other patient not included in this series, who had a pulmonary embolus following treatment with penicillin in wax by injection.

COMMENT

The results obtained in this study indicate that penicillin in oil and wax is as effective in the treatment of early syphilis as aqueous penicillin. There were 11 (18.9 per cent) patients for whom treatment failed among 58 patients treated for primary and secondary syphilis and 4 (23.4 per cent) with relapse among the 17 patients with recurrent syphilis. Thomas, Landy and Cooper[1b] obtained similar results in a large number of patients with early syphilis. These workers used doses of 4,800,000 units of penicillin in oil and wax in eight days. The number of patients with relapse or reinfection in their series after follow-up of at least six months was 13 per cent of 392 patients treated for primary and secondary syphilis and 37 per cent of 30 patients who had had previous treatment for syphilis. Although the dose of penicillin in oil and wax used by Thomas and his associates was half that given to the patients in this study, the results do not appear to be significantly different. This is not surprising, however, for studies of treatment with aqueous penicillin in early syphilis have shown that there is little difference in the results obtained when doses greater than 2,400,000 units are given. It seems probable that the amount of pencillin used in my patients was excessive and that smaller doses may be equally effective.

Injections of penicillin in oil and wax given twice a week appeared to be as effective as daily injections of the drug. This observation was of

3. Sheldon, W. H., and Heyman, A.: To be published.

4. Bondy, P. K.; Sheldon, W. H., and Weens, H. S.: Pulmonary Embolism Caused by Penicillin-Oil-Beeswax; An Experimental Investigation with Report of a Near-Fatal Case, Am. J. Med. 3:34, 1947.

interest, since little or no penicillin remains in the patient's blood thirty-six to forty-eight hours after the injection of 600,000 units of penicillin in oil and wax. Experiments with syphilis in rabbits, however, have suggested that constant maintenance of measurable levels of penicillin may not be necessary in treatment for syphilis.[5] It would appear, therefore, that strict adherence to daily treatment with penicillin in oil and wax may not be necessary and that more convenient schedules of two or three injections a week may be successfully employed.

The number of untoward reactions encountered with treatment with penicillin in oil and wax is somewhat greater than with treatment with aqueous penicillin. The most troublesome reactions were local pain and urticaria. The latter responded well to the administration of diphenhydramine hydrochloride, and the simultaneous use of this drug with penicillin in oil and wax was successful in preventing recurrence of this reac-

Results of Treatment with Penicillin in Oil and Wax (9,600,000 *Units*)

	Total No. of Patients	Treatment Failure	Sero-negative Reaction	Sero-positive Reaction
Primary syphilis	14	3*	11	0
Secondary syphilis	44	8*	30	6
Recurrent syphilis	17	4	11	2
Total	75	15 (20%)	52 (69.3%)	8 (10.6%)

*At least 1 of these patients appeared to be reinfected.

tion. Treatment had to be discontinued in only 1 patient, and this was the patient with pulmonary emboli. This accident occurred despite the usual precautions observed in injecting insoluble material. Although similar episodes have not been experienced in other clinics in which large quantities of penicillin in oil and wax have been used,[6] it is certainly a danger and care must always be employed in administering this drug.

The cost of the large amounts of penicillin in oil and wax required for the treatment of early syphilis is not excessive, considering the cost and inconvenience of hospitalization necessary with the use of aqueous solutions. Ambulatory schedules with pencillin in oil and wax, however, have one disadvantage, with respect to a large clinic group, and that is the occurrence of delinquency, particularly if treatment is prolonged to eight weeks or more. Several of my patients missed one or more

5. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis, Bull. Johns Hopkins Hosp. **79**:168, 1946.

6. Thomas, Landy and Cooper.[1b] Romansky, M. J.: Personal communication to the author.

treatments, and it was only by constant case-holding efforts that I was able to obtain completion of treatment in all of the patients.

SUMMARY AND CONCLUSIONS

A group of 78 patients with primary and secondary syphilis were treated on an ambulatory basis with 9,600,000 units of penicillin in oil and wax. Fifteen (20 per cent) of the patients followed up for six to nineteen months presented evidence that treatment had failed.

The commonest reactions to treatment with penicillin in oil and wax were local pain, urticaria and eosinophilia.

Penicillin in oil and wax appears to be as effective in the treatment of early syphilis as aqueous penicillin and provides a convenient method of treating this stage of the disease.

36 Butler Street, S. E.

KERATOSIS PILARIS RUBRA ATROPHICANS FACIEI

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CLEVELAND

REPORT OF A CASE

A WHITE girl, R. J., 16 years old, was first seen in July 1940. The condition of her skin had been present since early childhood and had not changed much. As shown in the genealogic chart, it was a hereditary condition and had resisted every type of treatment up to the time of examination. The photographs show the condition better than any description could. The profile view is identical with the picture in "Nouvelle pratique dermatologique."[1] There were two different conditions of the skin present. The maxillary regions of both cheeks showed pigmentation of different shades, forming a network of light and dark brown flecks. The whole region was affected, without a single spot of normal skin inside the border on both cheeks. Close observation revealed fine scarring intermingled with small areas of chronic dark red inflammation. There was no facial down visible in the entire affected area. The middle of the forehead showed a similar change of the skin; however, this was less pronounced. The scars were not so definite, and the follicular origin was more noticeable than on the cheeks. The affected area was of triangular shape, with the apex between the eyebrows and descending to the bridge of the nose. There were never any leisons present in the eyebrows.

There was a second feature of the disease, which has not been described in the few published cases of this disease. The areas of both cheeks adjoining the nose were covered with large pores. The location was symmetric. The openings were wide, as can be seen in the full face photograph. There was no inflammation or scarring visible. This condition had also been present since early childhood. On the extensor surface of the arms and legs, the skin showed the typical picture of lichen pilaris.

Genealogic Data.—The mother of the patient, 36 years old, presented the same condition as described except that it was not so well defined.

From Mount Sinai Hospital, Cleveland.

1. Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 7, p. 89.

A younger sister, aged 13, had a normal skin. This girl resembled her father more than her mother. The youngest child, a sister who was 11 years old, had the same condition as R. J.; however, it was even less pronounced than the mother's condition. According to the family history the disease was passed on by the great-grandfather and the grandfather.

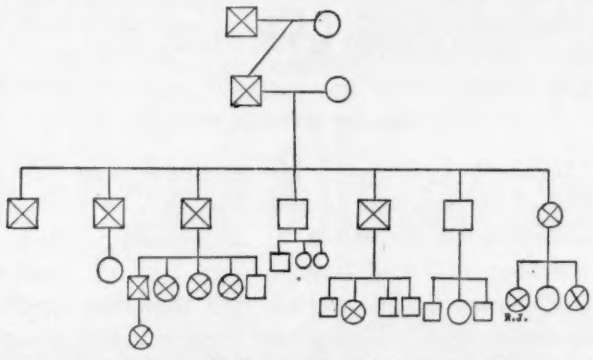

Fig. 1.—Genealogic chart of the family of R. J., showing the incidence of keratosis pilaris rubra atrophicans faciei.

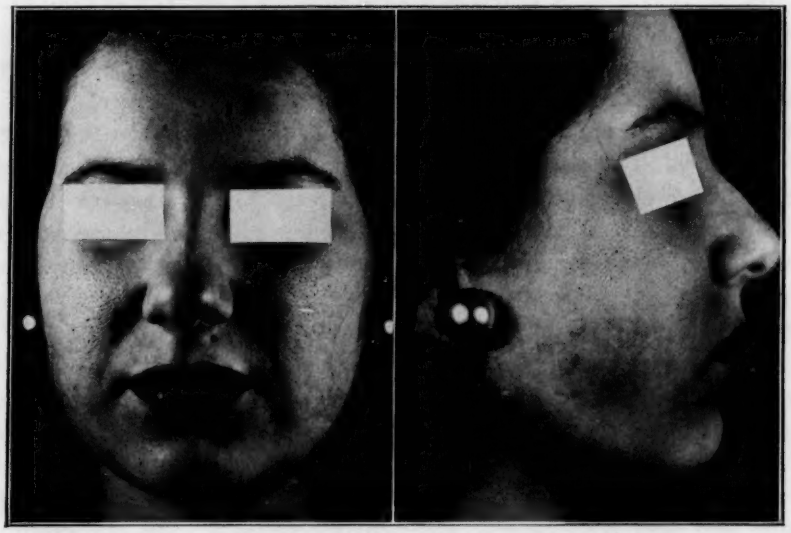

Fig. 2.—Front and profile views of R. J., showing the extent of the disease on the face.

The grandfather had had 7 children, 6 boys and 1 girl, the mother of the patient. Two of R. J.'s uncles did not have the disease. Only 3 of the other men afflicted with the disease had families. An uncle, twelve years older than R. J.'s mother, had 5 children, of whom 4 had the same disease. The oldest one, a man, was married and had a small daughter, who had the disease. The other 3 children of this family who were af-

flicted were girls. Another married uncle who had the disease had 4 children, 3 boys and 1 girl. Only the girl had this disease. In a survey of the five generations, as can be seen from the chart, both sexes in about the same proportion had the disease. However, in the fourth generation, a predominance among the female members is apparent.

CLINICAL DESCRIPTION

In 1889 Brocq[2] presented the case of a 10 year old girl with a disease diagnosed as *keratose pilaire* or *xerodermie pilaire symmetrique de la face*. The patient had had, as an infant, a psoriasis-like eruption. The present disease had started when she was 3 or 4 years old and had developed slowly. When the patient was first seen, in 1888, there were two symmetric plaques on her forehead, above the eyebrows. Small elevations of the skin, which were pointed or slightly rounded at the top and more or less colored, were visible between the eyebrows and on the forehead outside the plaques. In the center of almost every one there was a lanugo hair. Groups of these papules and the inflammation from the two plaques extended over the eyebrows.

The dermatitis on the sides of the cheeks, however, did not have the same appearance. Here again were the small pointed elevations of the skin, one series adjacent to the next, forming two large symmetric lesions which occupied the entire side of the cheeks. There were fine vascular telangiectases. This new eruption was distinctly apparent near the ear. The lichenoid elevations were noticeable on the border of the plaque on the anterior part of the cheek. There were also some of these small elevations sprinkled over the margin of the jaw and the ear lobe.

When the patient's brother was 5 years old, he had the same disease in the area of the eyebrows and on the sides of the cheeks. Brocq saw 2 other cases of *lichen pilaire de la face* and described the development of the disease as follows:

(1) Beginning, in infancy; slow, gradual, and almost unnoticeable development.

(2) Distinctive localization: In the eyebrows, together with some thinning of the hair, and on the forehead over the eyebrows; on the sides of the cheeks and the adjacent parts of the neck; the region between the eyebrows, and the chin.

(3) Absolute symmetry.

(4) Thousands of tiny lichenoid, partly squamous eruptions in the center of which there are often lanugo hairs and which are entirely colorless and isolated. Later there is a tendency to form groups by multiplication of the original lesion which rarely increases in its size.

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2. Brocq, L.: Lichen pilaire ou zerodermie pilaire symmetrique de la face, Ann. de dermat. et syph. **10**:339, 1889; Notes pour servire a l'histoire de la keratose pilaire, ibid. **1**:25, 97 and 222, 1890; Quelques rémarques sur les alopecies de la keratose pilaire, Monatsh. f. prakt. Dermat. **15**:609, 1892; Alopecies, in La pratique dermatologique, Paris, Masson & Cie, 1901, vol. 1, p. 301.

(5) Finally a vascular component which is purely erythematous and appears where there are multiple lichenoid eruptions. This later becomes very marked and some slight swelling of the skin occurs. Telangiectasis develops very quickly on the side of the cheeks. This gives the affected parts a somewhat purplish tinge.

It is interesting to note that Brocq mentioned that Wilson,[3] in his lectures on dermatology in 1878, described the disease and called it "folliculitis rubra." He gave the following description:

There is a distinct form of hyperaemic congestion or subacute inflammation of the follicles which is associated with the congenital malnutrition and feebleness of the skin. It is restricted to the follicles and its identity is easily determined by the presence of red puncta, more or less prominence of the aperture of the follicle, and a loaded state of its excretory duct, which is distended with epithelial exuviae. Its seat is also pathognomonic; the eyebrows, the maxillary region of the cheeks, and the back of the upper arms and, from its self-evident pathological nature, it has seemed to me to be well expressed by the term "folliculitis rubra."

Folliculitis rubra is met with in children and young persons, more particularly in those of the female sex and occasionally in the adult. It is at once recognized by a suffused redness of the lower part of the forehead, the eyebrows, and side of the cheeks, and, if from these parts, we proceed to the back of the upper arms, we shall very probably find them bright red in color and studded with minute papulae closely patched together looking like obliterated follicles and communicating a sense of roughness to the hand when passed over them. . . A closer examination detects the depth in the skin to which the hyperaemia extends; and the minute plugs of loosened epithelium afford evidence that the whole extent of the follicle is involved. Moreover, a still more important sign presents itself; the hairs growing from the follicles have, many of them, fallen out and in the course of time the eyebrows will become entirely denuded, the outer half first and then throughout the rest of their length. . . .

Cause. The cause of this state of the skin is, essentially, defect of nutrition power operating in a congenital and sometimes hereditary weak skin. I was much struck with the presence of this affection in a family of three or four young ladies, the daughters of a gentleman whom I knew to be the subject of ichthyosis, with which defect of the skin folliculitis rubra is closely aligned . . . Folliculitis rubra is very little amenable to treatment and often resists our best endeavors to promote its cure.

The relationship between keratosis pilaris rubra atrophicans faciei and ulerythema ophryogenes is sometimes mentioned. Some authors[4] described cases in which apparently both of these diseases were combined in 1 patient. It seems necessary to refer to the original paper of Taenzer,[5] in which the first description of ulerythema ophryogenes was published and which referred to it as "a skin disease undescribed up to the present

3. Wilson, E.: Lectures on Dermatology, London, J. & A. Churchill, 1878, pp. 217-220.

4. (*a*) Siemens, H.: Dermat. Wchnschr. **112**:281, 1941. (*b*) Moncorps, C., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927-1932, vol. 8, pt. 2, pp. 109-110.

5. Taenzer, P.: Ueber das Ulerythema ophryogenes, eine noch nicht beschriebene Hautkrankheit, Monatsh. f. prakt. Dermat. **7**:197, 1889.

[1889]." Taenzer reported 6 cases, 3 of them in the same family, and accentuated the characteristic features of the disease as follows:

> The beginning in earliest youth with reddening of the skin of the eyebrows which later spreads over the neighboring parts of the skin especially the face and the scalp but only very rarely over the upper arms. The picture is one of nonpurulent folliculitis which ends in atrophy of the skin.

The cases described were of a 40 year old mother, her 10 year old daughter and her 1 year old son, a 20 year old girl and her 8 year old brother, a 31 year old man and an 11 year old boy. In all these cases, the disease started in the eyebrows, and Taenzer proposed the name ophryogenes (superciliare) to make it clear that this is a special disease.

COMMENT

Brocq presented his first case of this disease in February 1889, at a meeting at the Hôpital St. Louis. One year later, he published a paper with remarks about the history of "keratosis pilaris." He supplemented this with a paper which he read at the second International Congress of Dermatology in Vienna in 1892. There have been few cases published since that time outside France.

Halter[6] described a case in a 42 year old man, with small lesions and slight atrophic changes in the eyebrows, cheeks and skull. The patient described by Gaté, Cuilleret and Boyer[7] was an 8 year old girl with acne decalvans, keratosis pilaris atrophicans et onychogryphosis of the toes. Salin presented a case in which the diagnosis was keratosis pilaris rubra atrophicans faciei plus granulosis rubra nasi. A family with the same discase was described by Covisa, Bejarano and Gay.[8] Two girls, 15 and 16 years old, respectively, were presented by Siemens, with a disease diagnosed as lichen pilaris and ulerythema ophryogenes. Klumpp[9] presented a case in which the diagnosis was "keratosis pilaris"; Jack Wolf remarked that this clinical picture was described under the name "keratosis pilaris rubra atrophicans" by Brocq.

Anderson[10] presented a 3½ year old white boy with the same disease, with the remark that 2 other young children of the same family had a similar eruption.

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6. Halter, K.: Keratosis pilaris rubra trophicans; Urticaria, Zentralbl. f. Haut- u. Geschlechtskr. **57**:5, 1937.

7. Gaté, J.; Cuilleret, P., and Boyer, C. E.: Acne decalvante: Keratose pilaire atrophiante et onychogryphose des orteils, Bull. Soc. franç. de dermat. et syph. **38**:1033, 1931.

8. Covisa, J. S.; Bejarano, J., and Gay, P. J.: Hereditary Keratosis, Pilaris, Rubra Atrophicans of the Face, Actas dermosif. **19**:171 and 254, 1927.

9. Klumpp, M. M.: Keratosis Pilaris, Arch. Dermat. & Syph. **46**:904 (Dec.) 1942.

10. Anderson, N. P.: Keratosis Pilaris of the Face, Arch. Dermat. & Syph. 49:81 (Jan.) 1944.

Returning to the description given by Wilson and later by Brocq and the description given by Taenzer and Unna regarding ulerythema ophryogenes, it seems that these are two different conditions, each of which has a specific primary location and a typical course. However, there are combinations of the two which may occur in the same person, but one or the other of the diseases will dominate.

It should be kept in mind that ulerythema ophryogenes always starts in the eyebrows, apparently from an infection of the hair follicles, which progresses slowly and forms typical folluculitis with pus.

Keratosis pilaris rubra atrophicans faciei starts in the preauricular region of the cheeks and forehead, with slow primary infiltration of the hair follicle which never shows formation of abcesses (acute folliculitis). The inflammation progresses slowly during the years, invades the normal skin and forms scars. Since the development proceeds slowly, the varying degrees of atrophy produce a netlike appearance. As a consequence of the chronic inflammation, all hairs disappear in the diseased region. The disease never reaches the skin on the cheeks adjacent to the nose.

TREATMENT

Vitamin A capsules, 100,000 to 150,000 units a day, and iron pills were administered internally. External treatment consisted of the administration of ultraviolet rays, daily baths in water to which sodium bicarbonate had been added and the use, after drying, of an ointment made of cod liver oil, salicylic acid and tar oil in a base of wool fat and petrolatum. There was temporary improvement; however, as soon as the treatment was stopped the cutaneous condition returned to its former state. As for the preauricular regions, they did not become worse during the four years of observation; therefore, their condition seemed to be always the same.

SUMMARY AND CONCLUSIONS

A family with typical keratosis pilaris rubra atrophicans faciei is presented, and the condition of the oldest child is described in detail. After reviewing the literature, it seems clear that there exist two cutaneous conditions, both of which may be hereditary. However, each is an entity with distinctive features. Both start in early youth, one at the temples and the other in the eyebrows. All of the patients also had keratosis pilaris on the typical locations of the body. There may be combinations of both; however, keratosis which starts in the eyebrows in early youth should always be designated ulerythema ophryogenes, whereas, keratosis pilaris, with reddening of the skin and later scarification, which starts outside the temples, in front of the ears, should be called keratosis pilaris rubra atrophicans faciei. The cause of both these diseases is unknown as yet, and no effective treatment has been published.

AMINOPHYLLINE AS AN ANTIPRURITIC AGENT

III. Comparison with Certain Other Theophylline Salts

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THE ANTIPRURITIC action of the parenteral administration of aminophylline (theophylline ethylenediamine) has been described in previous discussions.[1] This communication is concerned with the comparison of this agent with certain other salts of theophylline. Briefly, it has been demonstrated that many vasodilators, including xanthine derivatives and others, have similar effects on itching. This group includes various theophylline salts, procaine hydrochloride, papaverine hydrochloride, nicotinic acid and calcium. Lundy[2] injected procaine hydrochloride intravenously to relieve the itching of jaundice. State and Wangensteen,[3] using this agent in the treatment of delayed serum sickness, demonstrated that procaine hydrochloride given intravenously acts as a vasodilator. Wirth[4] pointed out that papaverine hydrochloride, which is also a vasodilator, has antipruritic properties. Service[5] observed nicotinic acid injected intravenously to be of benefit in urticaria and certain related conditions due to penicillin. Calcium, which also has vasodilating properties, is often used as an antipruritic agent.

Obviously vasodilation does not relieve itching. Mechanical vasodilation does not stop itching. Scratching and heat may aggravate the symptoms. Vasodilators that act locally, such as counterirritants, also increase the severity of pruritus. Drugs that produce vasodilatation on local administration, such as histamine, may also cause itching. Cutaneous entities associated with dilatation of the involved blood vessels, as exem-

1. Epstein, E.: Theophylline Ethylenediamine as an Antipruritic Agent: Preliminary Report, Arch. Dermat. & Syph. **53**:281 (March) 1946; Aminophylline as an Antipruritic Agent: II. Intramuscular Injection, ibid. **56**:373 (Sept.) 1947.

2. Lundy, J. S.: Clinical Anesthesia, Philadelphia, W. B. Saunders Company, 1942, pp. 392-393.

3. State, D., and Wangensteen, O. H.: Procaine Intravenously in Treatment of Delayed Serum Sickness, J. A. M. A. **130**:990 (April 13) 1946.

4. Wirth, L.: Antipruritic Qualities of Papaverine Hydrochloride, J. Invest. Dermat. **8**:63 (Feb.) 1947.

5. Service, W. C.: Use of Nicotinic Acid in Treatment of Urticaria Due to Penicillin, Ann. Allergy **4**:397 (Sept.-Oct.) 1946.

plified by urticaria, are often characterized by pruritus. Therefore ,it seems likely that mere enlargement of the blood vessels does not relieve itching.

According to the consensus, the end organs and nerve fibers conveying impulses of itching are the same ones that carry pain sensations.[6] Pruritus is considered to be a subpain sensation. However, the evidence presented by this work with vasodilators suggests that the "itching center," if such a center is ever demonstrated, may be more closely related to the vasodilator center than to the pain centers in the brain.

COMPARISON OF THEOPHYLLINE SALTS

Itching is a subjective symptom that defies accurate measurement. Therefore, clinical impressions must be employed in evaluating results of treatment. Such measurements are notoriously inaccurate, because of personal feelings on the part of both the patient and the physician. However, the following impressions are based on the observations made by the presenting investigator in this group of patients.

Aminophylline.—The previous communications were concerned exclusively with this agent.[7] The results obtained in the alleviation of pruritis were considered to be promising but evanescent. The dangers of treatment with this drug, both disconcerting immediate reactions and possible fatalities, were reviewed. The more prolonged, but less dependable, benefits of intramuscular injection were also presented. The severe local reactions accompanying the latter route were stressed. Further studies with this agent have confirmed previously reported observations. However, the results obtained in 30 previously unreported cases of various pruritic dermatoses treated with intravenous injection of aminophylline are presented.

A dose of 0.5 Gm., administered in 20 cc. of diluent, was utilized in this series. Fifteen patients suffered with contact dermatitis, the disease in 11 being due to poison oak, in 2 to local medication and in 1 to geraniums; in 1 the cause was undetermined. There were 17 women and 13 men. Twenty-eight of the patients were white, the other 2 being Negro. The ages ranged from 15 to 64 years. Nearly 70 per cent of the patients were between 20 and 39 years of age.

Immediate complete relief was obtained in 24 patients (80 per cent). In these 24 patients the itching was stopped for an average of ten and eight-tenths hours. However, in some instances the freedom from itching

6. Sulzberger, M. B.: Pruritus and Its Treatment, M. Clin. North America 19:971 (Nov.) 1935.

7. The aminophylline used in this study was furnished by the Endo Products, Inc., Richmond Hill, N. Y.

lasted less than a half-hour. In 58.5 per cent of the cases, the relief lasted more than eight hours. The duration of relief varied in the same patient from injection to injection. The 30 patients received an average of two and seventh-tenths injections each. The maximum number of injections given to any patient was ten. It should be stated that the severity of immediate reactions limited the number of injections that any patient would take. The immediate symptoms included prickling sensations, syncope, dyspnea, nausea, vomiting (in 1 case) and tachycardia. In some patients, these symptoms persisted for hours.

Attempts were made to minimize these disconcerting reactions by increasing the dilution of the theophylline salt. Four patients were given 0.5 Gm. of aminophylline in 1,000 cc. of 10 per cent dextrose, with elimination of the immediate symptoms but without antipruritic effect. Six patients were given the same dose of aminophylline in 50 cc. of 10

Comparison of Results Obtained with Aminophylline, Theophylline Monoethanolamine and Theophylline Methylglucamine

	Aminophylline	Theophylline Monoethanolamine	Theophylline Methylglucamine
Number of patients	30	8	9
Number immediately and completely relieved	24(80%)	6(75%)	4(44.5%)
Average complete relief	10.8 hr.	7.3 hr.	5.7 hr.
Number of injections received by each patient	2.7	2.5	10.2

per cent dextrose, without significant changes in the rate and severity of the reactions. On the other hand, the therapeutic effect was lessened. Only 2 patients (33.3 per cent) experienced immediate cessation of itching. Furthermore, in these 2 patients, the relief lasted for an average of only four hours. One patient suffered a severer reaction with this dilution than with the same dose given in 20 cc. of diluent. On the whole, any decrease in reactivity could be attributed to the slower injection resulting from the increased volume of fluid administered.

Theophylline Monoethanolamine.—This agent[8] was tested in 8 cases. The dosage was 0.5 Gm. administered intravenously in 20 cc. of diluent. The reactions and therapeutic results were similar to those obtained with aminophylline. Immediate relief was noted in 6 instances (75 per cent). The freedom from pruritus averaged seven and three-tenths hours in these patients. An average of two and five-tenths injections was given to this group.

8. The theophylline monoethanolamine used in this study was furnished by Eli Lilly and Company, Indianapolis.

From this it can be seen that this agent has antipruritic properties. Although this series is too small to be significant, the impression was gained that this drug is slightly less effective than aminophylline.

Theophylline Methylglucamine.—Nine patients with various itching dermatoses were treated by the intravenous injection of this agent[9] in doses of 0.732 Gm. in 20 cc. of diluent. These patients received an average of ten and two-tenths injections, attesting to this drug's lesser reactivity in comparison with the two previously discussed theophylline compounds. Immediate complete relief was obtained in only 4 cases (44.5 per cent), signifying the definite, but less frequent, therapeutic results. In the 4 patients who obtained relief, the effect lasted an average of five and seven-tenths hours.

Comparison.—In the table, comparison of the aforementioned agents is made. It demonstrates that aminophylline is probably the most effective agent of this group. Theophylline methylglucamine produces the fewest reactions. All three agents have definite antipruritic properties.

COMPARISON OF DERMATOSES

Of the 30 patients treated with aminophylline, 15 presented contact dermatitis. In 10 of these patients (66.6 per cent), the relief lasted more than eight hours. In 3 (20 per cent), immediate complete relief was obtained, but the freedom from itching lasted less than eight hours. In the other 2 patients (13.4 per cent), no results were obtained.

Two patients with fairly generalized atopic eczema were treated. Both experienced immediate relief. In 1, the relief lasted more than eight hours. Five patients with localized eczema, as on the hands, were treated with intravenous injection of aminophylline. All 5 were immediately relieved of the itching. However, this lasted for more than eight hours in only 2 instances.

Two patients with scabies were treated with little success. Similar results were obtained in 2 patients with lichen planus. The results of treatment with this agent in 1 case each of urticaria and of pruritus ani were also disappointing. One patient with toxic dermatitis and 1 with flea bites reacted more favorably to this treatment.

This series is too small to be significant, but in a general way supports the impression that theophylline salts are more valuable in acute than in chronic pruritic conditions.

COMMENT

Treatment with neither aminophylline nor any of the other vasodilators mentioned in this communiction can be considered to be the ulti-

9. The theophylline methylglucamine used in this study was furnished by Abbott Laboratories, North Chicago, Ill.

mate antipruritic technic. It is felt that these drugs represent substantial improvement over the other local, oral or parenterally administered remedies for itching. However, there are many related drugs to be studied in the hope of locating an ideal treatment for pruritus.

These agents apparently aid healing by disrupting the vicious cycle of itching leading to scratching, with more itching followed by further trauma. In a previous paper,[1a] it was noted that healing occurred more quickly once the psychic and physical trauma of scratching was eliminated. This is of value in acute dermatoses, such as contact dermatitis. However, in chronic pruritic conditions, the relief of itching is only temporary, and the return of the pruritus and the resulting trauma reduce the patient to his pretreatment status. It is possible that, if this drug were given every four hours, even chronic eczematoid reactions would heal in a short period of time. However, the necessity for careful intravenous injection makes this impossible in private practice.

The value of the agents tested so far is limited by a combination of factors, including the necessity for intravenous administration, the annoying and possibly serious reactions and the evanescence of results. On the other hand, this approach offers great promise. The action is suggestive of that of morphine on pain. The desired effect is usually, but not always, obtained; it lasts about ten hours and is of symptomatic value.

Therefore, this communication should be considered as suggesting an approach to the problem of pruritus, but not the final solution.

SUMMARY

Evidence is presented demonstrating that the intravenous injection of certain vasodilators (theophylline salts, procaine hydrochloride, papaverine hydrochloride and others) may result in immediate complete relief of itching.

Aminophylline (theophylline ethylenediamine) seemed to be more effective than either of the other two theophylline salts studied.

Immediate complete relief of itching occurred in 80 per cent of the 30 patients treated with aminophylline, and this freedom persisted for an average of ten and eight-tenths hours.

These agents are more valuable in acute than in chronic pruritic dermatoses.

447 Twenty-Ninth Street.

FAMILIAL URTICARIA DUE TO COLD

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THE APPEARANCE of urticarial wheals following exposure to cold is relatively common. Cooke[1] mentioned the case of Pepys, who suffered an attack of urticaria while walking in the park on a cold day in February 1663. Bourdon[2] in 1866 described urticaria and syncope due to cold, and in the same year Behier[2] described his own urticaria following exposure to cold. In an exhaustive study in 1936, Horton, Brown and Roth[3] were able to find 76 cases in the literature in which hypersensitiveness to cold was described.

Jadassohn and Schaaf[4] reported the cases of a brother and a sister in whom wheals developed following exposure to cold. These urticarial lesions were chiefly confined to the hands and face. Kobacker and Parkhurst[5] reported 3 sisters, in 1934, who had measles simultaneously. Shortly after their recovery it was noticed that these children would experience localized urticarial wheals following contact with a cold object. This sensitivity subsided and had completely disappeared at the end of one year.

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1. Cooke, R. A.: Allergy in Theory and Practice, ed. 1, Philadelphia, W. B. Saunders Company, 1947.

2. Cited by Horton, Brown and Roth.[3]

3. Horton, B. T.; Brown, G. E., and Roth, G. M.: Hypersensitiveness to Cold, with Local and Systemic Manifestations of Histamine-Like Character: Its Amenability to Treatment, J.A.M.A. **107**:1263-1269 (Oct. 17) 1936.

4. Jadassohn, W., and Schaaf, E.: Kälteurtikaria bei zwei Geschwistern, Dermat. Wchnschr. **86**:565-566 (April 28) 1928.

5. Kobacker, J. L., and Parkhurst, H. J.: Cold Urticaria Following Measles in Three Sisters, J.A.M.A. **105**:662 (Aug. 31) 1935.

No case had been reported in which cold urticaria was due to a familial trait until 1940. Kile and Rusk[6] gave a report of a patient in whom typical urticaria developed after exposure to cold. This was accompanied with fever and joint pains. In their case the family history revealed that 23 out of a total of 47 known relatives had this same allergy to cold. This familial trait had been present for at least five generations.

Urbach, Herrman and Gottlieb[7] gave the history of a 22 year old man who had attacks of urticaria, fever and visible swelling of the joints after exposure to cold air. This phenomenon had begun at birth, and 16 others out of 24 known members of his family had been similarly affected.

We add a third case in which there was an extensive family history; the patient was seen at a United States Army hospital.

REPORT OF A CASE

A 19 year old white soldier was admitted to Oliver General Hospital on Nov. 19, 1946, with a chief complaint of urticaria and joint pains following exposure to cold. This soldier was a native of South Carolina and had never been out of the "deep" South prior to his Army service.

History.—When the patient was 3 weeks old, it was noticed that his skin turned blue on exposure to cold and a few hours later the affected areas became erythematous. In childhood, wheals resembling urticaria developed on the erythematous eruption. Pruritus had never occurred with this wheal formation, although a mild burning sensation was sometimes present. This cyanosis, followed by the urticarial rash, was accompanied with dull joint pains, the severity depending on the extent of the cutaneous reaction. Despite the warm climate in which he lived he noted that he was hindered in his school work by the presence of this affliction, which was so incapacitating that it necessitated the loss of one to two days a week during the cold months of the year. During the attacks of urticaria and arthralgia the patient suffered from chills and a slight elevation of temperature, and as he grew older the attacks became worse.

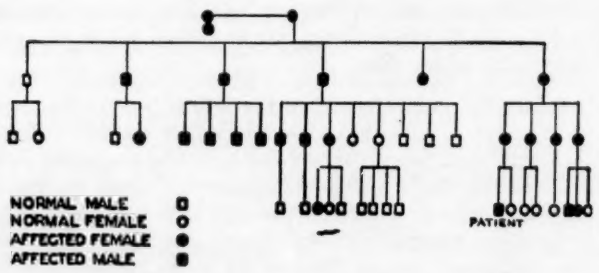
Induction into the Army took place on January 5, at Keesler Field, Miss. While undergoing basic training on the warm Gulf coast, this soldier required hospitalization for ten days because of this idiosyncrasy to cold. On being transferred to Scott Field, Ill. he was hospitalized for an additional seventeen days. During the summer of 1946, this patient was symptom free and later was sent overseas, arriving in Japan on October 1. While driving a truck in cold weather he experienced joint pains, accompanied with chills, and fever and cyanosis of his upper and lower extremities. Symptomatic treatment brought about immediate relief. Several nights later he was again exposed to cold and wind, became ill and was hospitalized. Arthralgia was the chief complaint on admission, and a temperature of 101 F. was noted. Wheals, 1 to 2 cm. in diameter, appeared on an erythematous base, involving the hands, forearms, feet and legs. Pruritus was

6. Kile, R. L., and Rusk, H. A.: Case of Cold Urticaria with Unusual Family History, J.A.M.A. **114**:1067-1068 (March 23) 1940.

7. Urbach, E.; Herrman, M. F., and Gottlieb, P. M.: Cold Allergy and Cold Pathergy, Arch. Dermat. & Syph. **43**:366-374 (Feb.) 1941.

absent, but during regression of the lesions stinging and burning was noticed. It was then decided that this patient was manifestly unfit for service; he was therefore returned to the United States. In the past this man had suffered from only those diseases common to childhood. He was told by his physician that he had "rheumatism," because of pain and swelling of the joints, fingers, wrists, elbows and ankles after exposure to cold.

Family History.—There is no family history of cancer, tuberculosis or disease of the heart, lungs or kidneys. The chart demonstrates the incidence of this syndrome for four generations, with 24 persons affected. The patient's mother was a semi-invalid because of this condition. The same type of eruption with varying degrees of joint involvement and elevation of temperature occurred in all those who were affected. It was notable that no child was afflicted with this condition whose parent did not have it. It invariably began in early childhood and persisted throughout life. Pruritus was lacking in all those affected, though varying degrees of stinging and burning were present. No member of this family had lived in the northern part of the United States, where the intense cold might cause a severer reaction. Interestingly enough no member of this family suffered from other forms of allergy.



Genealogic chart showing the familial incidence of urticaria due to cold in the case reported.

Laboratory Data.—Results of routine urinalyses and blood cell counts were always within normal limits. The sedimentation rate was 19 mm. Reactions to serologic tests for syphilis were negative. Prothrombin time, clotting time and bleeding time were determined, and all were normal. His basal metabolic rate was determined and was found to be +4 per cent. Roentgenologic studies of the chest and skull revealed no abnormalities.

Physical Examination.—The patient was a well developed and well nourished white man, 19 years of age. His height was 69 inches (about 175 cm.), and he weighed 180 pounds (about 82 Kg.). The epidermis appeared normal when first examined, but after exposure to cold the thighs and ankles were somewhat cyanotic, later becoming erythematous. Numerous wheals, from 1 to 2 cm. in diameter, appeared, with surrounding areas of blanching. These sometimes appeared on the trunk and upper extremities, but the sites of predilection were the inner surfaces of the thighs and the popliteal fossae. A few lesions of acne vulgaris were present on the face and shoulders, and mild tinea cruris was observed. The chest was clear to auscultation and percussion, and the heart was normal. The blood pressure was 120 systolic and 96 diastolic. Neurologic examination disclosed no abnormalities.

Course in Hospital.—It was observed that this patient was most likely to experience an urticarial eruption following exposure to cold wind. The patient slept on the porch of his ward on several occasions, and the lesions would invariably appear. After full development and after the patient was placed in a warm room, the lesions slowly regressed and were gone in four to six hours. It was observed that a slight elevation of temperature, of 0.5 to 1 degree, accompanied this eruption, and mild arthralgia was his only complaint. He was given 50 mg. of diphenhydramine hydrochloride ("benadryl hydrochloride") four times daily, with no apparent relief of the arthralgia or the urticaria. The dose was then increased to 100 mg. of diphenhydramine, four times daily, and with this increased dosage a slight improvement in the condition was noted. The only side effect of this drug was moderate sleepiness. The patient at no time complained of pruritus, and no attack observed by us was sufficiently severe to warrant his confinement to bed. It was felt that this patient was unable to perform military duty, and he was separated from the service.

COMMENT

There are many points of similarity in our case and the cases of Kile and Urbach. In all the families the condition appeared shortly after birth in those affected. The attack was brought on in every case by cold, wind or extreme changes in temperature. The same syndrome was present in all three groups—urticarial wheals, lack of pruritus, presence of a burning sensation, pain and swelling of joints, chills and mild fever. In the studies, slightly over 50 per cent of the members of each family were affected. The ingestion of cold liquids had no discernible effect on oral mucous membranes.

Cockayne[8] stated that in any allergic disease the number of affected male members of a family exceeds that of affected female members. It was noted by Kile that this was not true in his family study, and we noted that in both Urbach's and our cases the number of female members was greater.

SUMMARY

A case of familial urticaria due to cold in a 19 year old soldier is presented. There was an incidence of the identical syndrome in 24 out of 45 members of his family for four generations. Analogous studies have been made by Kile and Rusk[6] (1940) and by Urbach, Herrman and Gottlieb[7] (1941). So far as we know, this is the third such case to be reported in the literature.

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8. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, ed. 1, London, Oxford University Press, 1933, p. 364.

SALICYLANILIDE THERAPY IN TINEA CAPITIS

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AT PRESENT most dermatologists consider roentgen epilation the most efficient form of treatment for tinea capitis, particularly for the type caused by Microsporon audouini. In the last few years this fungus has been the predominant causative agent of the prevailing tineal infections of the scalp of children in the eastern and central parts of the country. On the basis of my experience with about 1,000 patients treated with roentgen epilation, I definitely support this view. In the hands of the skilled operator roentgen epilation is safe and effective. To many patients and their parents, however, any therapeutic measure that produces baldness for several months is still rather drastic and objectionable. Then, too, in many communities where the disease is prevalent this form of treatment is not available because of the lack of proper equipment and trained personnel. It is obvious, therefore, that there is still ample room in the armamentarium of dermatologists for simpler, and yet effective, agents for the eradication of this disease.

In the light of these facts the clinician who has been dealing with the problem of tinea capitis in the last few years has been faced with a twofold task. First, it was imperative that he institute promptly the best known curative and prophylactic measures in order to reduce the incidence of the disease and to return the children who had contracted the disease to their proper place in the community as quickly as possible. Second, the conscientious clinician was impelled at the same time to maintain a vigilant quest for simpler, and yet effective, curative agents. The first objective was reached mainly by the administration of epilating doses of roentgen rays to as many children as time and other factors permitted. In the search for other curative medicaments, an opportunity was afforded in the work with children whose parents or guardians refused treatment with roentgen rays, and desired other remedies. Another group was deliberately given a fair trial with one or more different medicaments in the clinic at Northwestern University before roentgen rays were administered. A third group of children afflicted with the disease

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had been treated with different topical applications before they were admitted to the clinic. In these circumstances one was able to observe the relative effectiveness of the different therapeutic agents used. The array of the various medicaments employed include well known substances in various strength and combinations, such as sulfur, salicylic acid, ammoniated mercury, mercury bichloride, tincture of iodine, iodine ointment, mercurochrome (5 per cent and 2 per cent solutions), benzoic acid, ointment of benzoic and salicylic acid, and the newer preparations, such as undecylenic acid, 5 per cent and 10 per cent ointment alone or in combination with zinc undecylenate, solution and ointment containing sodium propionate and propionic acid, a solution containing 1 per cent chlorazodin, solutions of dimethyl-benzyl-ammonium chloride, from 0.1 per cent to 3 per cent, and an ointment containing an antibiotic extracted from garlic. After months of trial with these remedies, only relatively few patients were really cured. The disease in many children showed favorable response at first, but, after reaching a certain point, remained utterly refractory to further treatment. Most of these patients were finally cured with roentgen epilation. Parents who refused treatment with roentgen rays struggled on with the topical applications for months and years, until either they changed their minds or time became a factor in the course of the disease.

The results obtained with the use of diethylstilbestrol, given daily in 0.5 mg. oral doses to 60 boys with tinea capitis, were disappointing. Results from the first few weeks of this treatment were encouraging, but after four to six weeks treatment with the drug had to be stopped because the breasts of the boys became swollen and tender. When the breasts returned to a normal state, resumption of treatment with the same drug failed to bring further improvement in the scalp. Out of a group of 50 boys treated with androgenic substances orally and parenterally, only 3 were cured. This group also showed improvement in the early part of the course, and then the disease remained stubbornly resistant to further male hormone therapy. A detailed report of the study made with diethylstilbestrol and androgenic substances in tinea capitis will be available in a separate communication.

In November 1945, Schwartz,[1] of the Section of Dermatoses, United States Public Health Service, reported the favorable results which he and his co-workers had obtained in the tinea capitis epidemic in Hagerstown, Md., with the use of an ointment containing salicylanilide 5 per cent in "carbowax 1500" (a mixture of polyethylene glycols having an average molecular weight of about 500). In September 1946, a more detailed report of this work was published.[2] From December to July 1946,

1. Schwartz, L.: Personal communication to the author.

2. Schwartz, L., and others: Control of Ringworm of the Scalp Among School Children, J.A.M.A. **132**:58-61 (Sept. 14) 1946.

this ointment was prepared in the clinic pharmacy and was given to the patients. From July to April 1947, an ointment containing the same ingredients and prepared in a local pharmaceutic laboratory was employed. This report deals with the results obtained in the treatment of 150 white patients with tinea capitis of the audouini type with the aforementioned ointment from December 1945 to April 1947, a period of approximately sixteen months.

CRITERIA FOR DIAGNOSIS AND CURE

A diagnosis of tinea capitis was made on the basis of the (1) history and clinical examination of the scalp and description of the lesion, (2) inspection of the scalp under the Wood light, (3) microscopic examination of the hairs mounted in 10 per cent sodium hydroxide or chloral lactophenol, (4) inoculation of Sabouraud's maltose agar slants with suspected hairs and (5) identification of the organism cultured.

A patient was discharged as cured when (1) after stopping all medication, three successive examinations under the Wood light, at least two weeks apart, failed to show the characteristic green fluorescence and (2) three separate inoculations of hairs on culture slants at least two weeks apart failed to show any growth characteristic of M. audouini.

The duration of treatment includes the six week period spent in observing the patients and cultures with the object of determining whether cure was effected.

METHOD OF TREATMENT

Each patient or parent was instructed as follows:

1. The hairs of the entire scalp must be clipped short to ⅛ inch (about 0.32 cm.) every ten days.

2. The ointment must be applied to the entire scalp once daily and to affected areas twice daily for three days.

3. The scalp must be washed on the fourth day and no ointment applied on that day. The three day treatment is resumed on the next day.

4. Tightly fitting caps made of boilable materials must be worn at all times. Fresh caps are supplied daily, and the old caps may be washed and boiled for five minutes every day with a solution of cresol added to the water.

5. The patient must present himself for examination at the clinic at least once every two weeks, and the scalp must be free from ointment at that time.

The progress of the disease was watched by biweekly clinical examinations and inspection of the scalp under the Wood light. Microscopic studies and cultures of the hairs were made during this period as conditions warranted them.

RESULTS OF TREATMENT AND COMMENT

Out of 150 white patients treated in the period of sixteen months, 124 were boys and 26 were girls. Of these, 105, or 70 per cent, were dis-

charged as cured; in this group there were 87 boys and 18 girls. The shortest period required to effect a cure was three months and the longest fourteen months, thus giving an average period of six and twenty-five hundredths months required for cure for the entire group of 105 patients. Seventy-six patients, 50.7 per cent of the entire group treated or 72 per cent of the 105 cured, were discharged within seven months. This period

TABLE 1.—*Number of Patients Cured and Duration of Treatment*

Months Required to Effect Cure	No. of Patients Cured	Percentage of 105 Patients Cured	Percentage of 150 Patients Treated
3	12	11.4	8.0
4	16	15.2	10.7
5	12	11.4	8.0
6	24	22.8	16.0
7	12	11.4	8.0
8	8	7.6	5.3
9	6	5.7	4.0
10	6	5.7	4.0
11	3	2.8	2.0
14	3	2.8	2.0
Totals	105		70.0

TABLE 2.—*Relationship of the Number and Size of Lesions to Duration of Treatment Before Recovery*

Group	Extent of Lesions	No. of Patients Treated	No. of Patients Cured	Percentage for Group	Average Time for Cure for Group (Mo.)	Improved 50 Per Cent Less Than 75 Per Cent	Improved 75 Per Cent	Improved More Than 75 Per Cent
I.	One to five small coin-sized lesions	48	48	100	4.8	—	—	—
II.	Not more than one fourth of scalp	32	32	100	6.6	—	—	—
III.	One fourth to one half of scalp	17	7	41	8.4	2	4	4
IV.	More than one half of scalp	53	18	34	8.6	5	20	10

of seven months is chosen because many boys treated with roentgen epilation experienced embarrassment and self consciousness for a similar period as a result of the baldness and irregular growth of hairs. During these months the boys tended to uncover their heads rarely and reluctantly, although the tineal infection was long since cured.

Table 2 demonstrates definitely that there was a direct relationship between the number and size of the lesions and the time required to

effect a cure. The 48 patients with a few coin-sized lesions averaged four and eighth-tenths months for cure. In the next group of 32, in whom involvement of the disease was limited to one fourth of the scalp, the time increased to six and six-tenths months for the group. All of the 80 patients in these two groups recovered fully in an average period of five and five-tenths months. As the lesions increased in size and involved more than one fourth or more than one half of the scalp, the average time for recovery increased to eight and four-tenths and eight and six-tenths months, respectively. Seventy patients had the severe form of the disease, and only 25 of them recovered fully in an average period of eight and five-tenths months.

The 45 patients in whom cure was not effected as of the date of writing belong to the third and fourth categories in table 2, in which the

TABLE 3.—*Relationship of Age of Patient to Duration of Treatment Before Recovery*

Age (Yr.)	No. of Patients	Average Time for Cure (Mo.)
1-2	4	3
3	12	7.0
4	20	6.0
5	8	6.5
6	20	7.4
7	4	8.0
8	8	10.0
9	16	6.4
10	4	5.0
11	3	7.0
12	1	4.0
13	2	4.0
14	3	3.0

disease process involved extensive areas of the scalp. Only 7 of these patients showed improvement of less than 50 per cent. Thirty-eight patients showed an improvement of between 50 and 75 per cent, while 14 patients showed improvement of over 75 per cent. Twenty of the 45 patients not cured had been receiving treatment from five to seven months; the other 25 had been treated for a period of seven to nine months. Judging by the rate of their improvement, one would be justified in predicting that some of these patients would recover fully in several more months.

From table 3 one may deduce that in both extreme ages of the group, the youngest and the oldest, the results were somewhat more favorable

than for the rest of the group. In the age groups of 1 to 2 years and 12 to 14 years, the average time required for cure was three to four months. In the largest number of the group, however, ages 2 to 10, the age of the child had no bearing whatsoever on the time required for cure.

Table 4 indicates that the duration of the disease before treatment was started does not influence the length of the period of treatment. A group of 12 patients that had had the disease for nine to twelve months before treatment was started required ten to eleven months to be cured, contrary to the notion entertained by many that patients whose tineal disease was of long standing recover more readily. On the other hand, another group of 8 patients that had had the disease for eight months before treatment was begun required an average of only three and one-half months for a course of treatment. Again it must be pointed out, then,

TABLE 4.—*Relationship of the Duration of the Disease to the Time Required to Effect a Cure*

Duration Before Treatment Was Started (Mo.)	No. of Patients Cured	Average Time of Treatment (Mo.)
1	4	6.0
2	8	5.5
3	34	7.0
4	15	6.7
5	4	8.0
6	8	6.0
7	12	6.3
8	8	3.5
9	8	10.0
12	4	11.0
Total	105	

that the severity and size of the lesions play the principal role in determining the time required for cure.

No unfavorable reactions were encountered from the application of this ointment. Occasionally the patients complained of slight irritation and tenderness of the scalp. These symptoms disappeared after a few days' rest. The ointment caused pronounced scaling of the scalp and gave the normal hairs a bluish gray tinge. The infected hairs were rendered more fragile and were easily broken. Under the Wood light the fluorescence of the diseased areas changed gradually with this treatment from bright green to dull bluish white. Later the hairs were slowly loosened and detached and became mingled in the debris covering the affected areas. When the adherent scales were removed, the underlying areas were observed to have definite thinning out of the diseased hairs.

Gradually the fluorescence in these areas became fainter, and eventually the remaining hairs ceased to give any fluorescence. Planting these hairs repeatedly on Sabouraud's maltose agar slants failed to produce any growth characteristic of M. audouini. In a few weeks normal hairs appeared and gradually filled in the areas that were partially bald.

None of the other topical applications or medicaments employed have given results comparable to the favorable results obtained with the use of this ointment in tinea capitis. In the mild and moderately severe forms of the disease this treatment compares favorably even with treatment with roentgen rays, if one gives proper consideration to the months of waiting for the regrowth of hairs. In the severe forms, however, epilation with roentgen rays was still a more efficient procedure.

CONCLUSIONS

1. Although epilation with roentgen rays is at present the most efficient form of treatment for tinea capitis of the Microsporon audouini type, simple effective therapeutic agents for this disease are definitely in demand.

2. The results obtained with a list of topical applications of old and new fungicides were entirely unsatisfactory.

3. Unfavorable results were obtained with diethylstilbestrol given orally to 60 boys with tinea capitis and with male hormone given orally and parenterally to 50 boys suffering from the same disease.

4. Treatment with an ointment containing 5 per cent salicylanilide in "carbowax 1500" (a mixture of polythylene glycols having an average molecular weight of about 500) effected a cure in 105 patients of a group of 150 white children with M. audouini infection of the scalp.

5. The shortest period required for recovery was three months, and the longest fourteen months, giving an average period of six and twenty-five hundredths months for the entire group of 105 patients.

6. Eighty patients whose tineal infection was limited to one fourth of the scalp were cured in an average period of five and five-tenths months.

7. Seventy patients had the severe form of this disease, and only 25 of them recovered fully in an average period of eight and five-tenths months.

8. Of the 45 patients that were not cured, 7 showed an improvement of less than 50 per cent. Fourteen of the remaining 38 patients whose disease improved showed over 75 per cent recovery.

9. The severity of the disease, as manifested by the size and number of lesions, was an important factor in determining the rate of recovery.

10. The duration of the disease before treatment was started and the age of the patient had only little bearing on the time required to effect a cure.

11. No unfavorable reactions from the use of this ointment were encountered.

12. Five per cent salicylanilide in "carbowax 1500" proved superior to all other topical applications and other medications employed in the clinic at Northwestern University in the treatment of tinea capitis. In the mild and moderately severe types of this disease this ointment gave results that compared favorably with results of epilation with roentgen rays. In the severe forms of tinea capitis, however, treatment with roentgen rays was still more efficient.

NOTE.—Since this paper was submitted for publication, the author encountered a small number of patients who showed a more violent reaction to the salicylanilide ointment than that described herein. In each instance after several weeks of treatment with the ointment the infected areas of the scalp became swollen, boggy and tender. The clinical picture resembled closely one of a kerion. When this occurred, mild topical therapy was substituted. All the patients with this type of reaction were completely cured within two to three months.

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USE OF VITAMIN A IN THE TREATMENT OF CUTANEOUS DISEASES

Relation to Estrogen and the Vitamin B Complex

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VITAMIN A is an unsaturated cyclic alcohol.[1] It has been extracted from natural sources and reduced to crystalline form,[2] and its synthesis has been reported.[3] The precursors of vitamin A are synthesized only by plants, as far as as is known,[1] and these substances, classed as carotenoids, function as photosensitive structures in plants.[4] In the animal kingdom, carotenoids are oxidized to vitamin A, and the vitamin is stored in the body. In some fish and mammals tremendous amounts of vitamin A are found stored in the liver and in the intestinal fat.[5] The purpose of these great stores is not known.

In the human organism, vitamin A is stored in the liver and carotene, after oxidization to vitamin A, is also stored. The conversion of carotene to vitamin A has been assumed to occur in the liver. However, it has been shown that in rats carotene can be converted to vitamin A only if it is given orally; after injection no conversion of vitamin A can be demonstrated, nor does the injection permanently cure a vitamin A deficiency.[6] It has been suggested that the intestinal wall may be the site

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of this conversion. The vitamin itself is of equal activity in rats whether given orally or by injection, although the type of solvent used for injection may alter the rate of absorption.[7]

Vitamin A is almost completely absorbed from the human intestinal tract under normal conditions.[8] After a test dose of 200,000 international units of vitamin A, an increase in the blood plasma of 300 to 500 international units occurs in three hours. There seems to be no relation between the maximum increase in the tolerance curve and the previous plasma level.[9] Normal levels of vitamin A in the plasma are usually concidered to be from 70 to 150 international units. While the plasma level may reflect a vitamin deficiency if the level is low, it does not usually indicate the amount stored in the liver. It was observed in rats that the level of vitamin A in the plasma was maintained until the stores in the liver were exhausted.[10] In 5 young men who were given a diet rich in vitamin A for thirty days, and then maintained on a diet extremely low in vitamin A for six months, levels of vitamin A in the plasma kept to their initial maximal levels for the entire period. Physical fitness was not impaired, and the visual threshold remained constant.[11]

Vitamin A is used more efficiently than is carotene. The absorption of carotene depends on the presence of bile salts and pancreatic lipase in the intestine.[12] About 60 per cent is excreted unchanged from the intestinal tract.[8] If large amounts are taken, the increase of carotene in the plasma may lead to the clinical appearance of carotenemia. The body seems to be unable to convert an excess to vitamin A and seems to have no mechanism to excrete the excess. The threshold quantity of carrots necessary to produce carotenemia is about 4 pounds (about 1,814 Gm.) of raw carrots per week for a period of seven months. After cessation of the carrot diet, the fading of the yellow color begins in two weeks and is complete in about eight weeks.[13] A baby fed only on the breast milk of its carotenemic mother had the condition in two months.

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The symptoms associated with carotenemia are usually mild: loss of weight and the appearance of yellowness most evident on the palms, soles and nasolabial folds. Results of the examination of patients with carotenemia by Anderson and Soley[14] suggested that an antagonism exists between carotene and thyroxin. In an excessive administration of vitamin A, on the other hand, the symptoms may be acute and severe. It has long been known by Arctic explorers and Eskimos that the ingestion of polar bear liver can cause severe illness. Symptoms of drowsiness and severe headache may occur within a few hours, and peeling of the skin around the mouth or on the whole body appears in the next twenty-four hours. Chemical examination of polar bear livers revealed them to be rich in vitamin A, and it seems likely that this is the cause of their toxicity. The livers examined contained about 20,000 international units of vitamin A per gram of wet liver, which would be 7,500,000 units in 3/4 of a pound (about 340 Gm.) of liver, presumably enough to cause a reaction.[15]

Josephs[16] reported the case of a boy of 3 years who had taken about 240,000 U.S.P. units of vitamin A as percomorph liver oil daily since he was 3 months old. He showed enlargement of the liver and of the spleen, hypoplastic anemia, leukopenia, advanced skeletal development and sparse coarse hair. The vitamin A of the plasma was 1,140 U.S.P. units. Most of the symptoms disappeared when treatment with the vitamin A was stopped; the hair became normal in two months, and by the end of six months the composition of the blood was normal. However, another child, 8 months old, who had taken 400,000 U.S.P. units daily for four months, appeared normal. The mechanism for controlling the level of vitamin A in the plasma may have been impaired in the first instance. It would appear that it is the amount of vitamin A which is in circulation, and can thus reach susceptible tissue, which determines the reaction. The vitamin A which is stored in the liver seems to be harmless, no matter how large the quantity.

From the vitamin A stores in the liver a greater amount disappears than that which is assumed to be needed for normal requirements. In the rat enough can be stored in the liver to meet theoretically ordinary requirements for a period of about a hundred years. However, vitamin A is lost rapidly with diets deficient in vitamin A. For several years Davies and Moore[17] tried to explain this observation. It was noted that rats re-

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17. Davies, A. W., and Moore, T.: The Interaction of Vitamins A and E, Nature, London **147**:794, 1941.

ceiving diets low in vitamin E had much lower reserves of vitamin A than those receiving supplements of vitamin E. Tests of this observation demonstrated that in rats with vitamin E supplements to diets deficient in vitamin A the stores of vitamin A in the liver decreased more slowly than in rats which did not receive the supplement of vitamin E.

It has been shown that tocopherol functions as an antioxidant in the gastroenteric tract to protect carotene and vitamin A.[18] This action depends on the presence of vitamin E in the tract itself, and it gives more protection if it is given at the same time as the vitamin A. Vitamin E also protects parenterally injected vitamin A, and the conclusion is that vitamin A is subject to destruction by the enzymes and oxidants in the intestinal tract both during absorption and as it circulates through the vascular system of the intestinal tract.

The bio-assay of fish oils containing vitamin A is done on rats raised specifically for this purpose. These rats are highly bred so that their growth requirements of vitamin A are fairly constant. Even so, the requirements vary with the basal diet, the season of the year and the amount of vitamin A administered per dose.[19] In human beings the requirements must vary widely, as they cannot be controlled by breeding, nor is the effect of the basal diet known. On the basis of experimental work on animals it would seem that 20 international units per kilogram of body weight is about the minimal requirement to maintain good light adaptation, but as light adaptation is probably a late manifestation of vitamin A deficiency, total amounts of 7,500 to 10,000 international units daily are advised.[20]

Vitamin A therapy has been of some benefit in certain rare cutaneous diseases which are also of a familial nature, namely, keratosis follicularis,[21] ichthyosis[22] and pityriasis rubra pilaris.[23] In patients with such dis-

18. Hickman, K. C. D.; Kaley, M. W., and Harris, P. L.; Covitamin Studies: The Sparing Action of Natural Tocopherol Concentrates on Vitamin A, J. Biol. Chem. **152**:303, 1944.

19. Muller, P., and Reinert, M.: Spectrographic Assay of Vitamin A and the Conversion Factor, Nature, London **157**:876, 1946.

20. Jolliffe, N., and Most, R. M.: The Appraisal of Nutritional Status, in Harris, R. S., and Thimann, K. V.: Vitamins and Hormones: Advances in Research and Applications, New York, Academic Press, Inc., 1943, vol. 1, p. 65.

21 (*a*) Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): A Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223 (Feb.) 1941. (*b*) Carleton, A., and Steven, D.: Dermatosis Follicularis: A Study of Four Cases, ibid. **48**:143 (Aug.) 1943. (*c*) Leitner, Z. A., and Moore, T.: Vitamin A and Skin Disease, Lancet **2**:262, 1946. (*d*) Peck, S. M.; Glick, A.; Sobotka, H. H., and Chargin, L.: Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease), Arch. Dermat. & Syph. **48**:17 (July) 1943.

22. Peck, S. M.; Glick, A. W., and Chargin, L.: Vitamin A Studies in Cases of Ichthyosis, Arch. Dermat. & Syph. **48**:32 (July) 1943. Rapport, H. G.;

(Footnotes continued on next page)

eases the results of plasma levels or of absorption curves do not consistently indicate a deficiency of this vitamin.[21c] When there is a deficiency of vitamin A, Frazier, Hu and Chu[24] have noted that follicular hyperkeratosis occurs most frequently at the time of puberty, when the endocrine glands are active in their effects on the skin. It has also been noted that, in attempting to determine vitamin A deficiency in rats by vaginal smear, the occurrence of estrus produces cornification indistinguishable from that of vitamin A deficiency.[25] It has also been observed that estrogens applied to the human scalp cause keratinization about follicles and atrophy of sebaceous glands.[26] All these observations suggest that the skin, altered by endocrine imbalance, is peculiarly susceptible and may demand great amounts of vitamin A for normal function. The following report of a case is pertinent in this regard.

REPORT OF A CASE

J. S., a woman aged 52 years, first noticed thickening and fissuring of the skin of her palms following severe sunburn when she was 16 years old. Her menstrual periods began at the age of 16 and were regular until the age of 46, when cessation was followed by symptoms of flushing and night sweats. The peeling of her palms recurred each summer and was at times accompanied with patches of roughness of the forearms and scaling of the scalp. All these lesions tended to disappear in the winter.

Six years prior to examination, at the time of the first menopausal symptoms, the scaling lesions did not disappear during the winter, and they have been continually present, despite varied local medication. When she was first seen, in January 1945, she had dry imbricated scaling on her scalp and her hair was dry and sparse. Her palms were keratotic and the finger tips were fissured. There was lichenification of the apposing areas of the buttocks. Flushes were of daily occurrence, but were controlled by estrogens given orally or by injection. In July a 5 cm. patch of follicular keratosis was seen on each forearm. Treatment with vitamin A, 100,000 units (Lederle Laboratories, Inc., vitamin A with 20 mg. of

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Herman, H., and Lehman, E.: The Treatment of Ichthyosis with Vitamin A, J. Pediat. **21**:733, 1942.

23. Brunsting, L. A., and Sheard, C.: Dark Adaptation in Pityriasis Rubra Pilaris, Arch. Dermat. & Syph. **43**:42 (Jan.) 1941. Weiner, A. L., and Levin, A. A.: Pityriasis Rubra Pilaris of Familial Type, ibid. **48**:288 (Sept.) 1943. Leitner and Moore.[21c] Porter, A. D., and Godding, E. W.: Pityriasis Rubra Pilaris and Vitamin A, Brit. J. Dermat. **57**:197, 1945.

24. Frazier, C. N.; Hu, C. K., and Chu, F. T.: Variations in the Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty, Arch. Dermat. & Syph. **48**:1 (July) 1943.

25. (*a*) Evans, H. M., and Bishop, K. S.. On the Invariable and Characteristic Disturbance of Reproductive Function in Animals Reared on a Diet Poor in Fat Soluble A, Anat. Rec. **23**:17, 1922. (*b*) Burrows, H.: The Biological Action of Sex Hormones, London, Cambridge University Press, 1945, p. 302

26. Rony, H. R., and Zakon, S. J.; Effect of Endocrine Substances on the Adult Human Scalp, Arch. Dermat. & Syph. **52**:323 (Nov.-Dec.) 1945.

vitamin E), was started. By September the follicular keratosis was discernible on the entire extensor aspect of the arms. The palms were unchanged. The soles have never been affected. In March 1946 her hair was thick and shiny, but the imbricated scaling of the scalp and the keratoderma of the palms were increasing. The vulva and intergluteal regions showed confluent redness and scaling, with definite borders. In June keratotic plugs, resembling nits, could be seen for several inches along the shafts of the hair of the scalp. This patient had been taking vitamin A, 100,000 units daily, for twelve months, but because of the lack of improvement, vitamin D, 100,000 units daily, was added along with ox bile, 3 Gm. daily. By August there was intense generalized itching, and the follicles of the trunk, arms and thighs appeared prominent by reason of a halo of pigmentation and a small central plug. Follicular spines appeared on the backs of the phalanges by August 15. The plugs increased in size and number, those on the abdomen and lateral aspects of the thighs reaching 4 mm. in diameter, and these were surrounded by induration and inflammation for about 1 cm. Because of the lack of response to orally administered vitamin A and the unquestionable diagnosis of pityriasis rubra pilaris, vitamin A was given by injection, 100,000 units in corn oil twice weekly. Improvement was noticeable within ten days, and within one month the follicular plugging had decreased and the skin was more pliable. On November 18 the patient was hospitalized for study. During her hospitalization the following vitamins were given orally each day: A, 200,000 units; E, 200 mg.; riboflavin, 10 mg.; thiamine, 9 mg.; nicotinic acid, 15 mg.; pyridoxine, 3 mg.; pantothenic acid, 30 mg.; inositol, 90 mg., and choline, 90 mg. Tests of hepatic function (cephalin-cholesterol flocculation and sulfobromophthalein sodium), tests of basal metabolism and examination of the blood and urine all gave essentially normal results. There was no family history of a similar disease of the skin.

During the two weeks of hospitalization the condition of the skin at first showed a little improvement, but at the end of the two weeks the follicular plugs had increased in size and the itching returned. On December 4 treatment with vitamin A by injection was again started, 100,000 units twice weekly; the response was evident within a week and continued, until by Feb. 21, 1947, the scalp and palms were normal, all inflammation had disappeared and there remained pigmentation about the follicles and some fine follicular spines in the follicles of the lumbar region. A vitamin A tolerance test was done on February 25 and showed a normal absorption curve: fasting results were 200 gammas of carotene, 104 international units of vitamin A; with 250,000 units of vitamin A in percomorph liver oil given orally, in three hours results were 181 gammas of carotene, 506 international units of vitamin A; in five hours results were 179 gammas of carotene, 1,221 units of vitamin A, and seven hours results were 183 gammas of carotene, 560 units of vitamin A. Because of the evidence of normal absorption of vitamin A as percomorph liver oil, it was decided to test the clinical response to this preparation. Two hundred thousand units of vitamin A, as percomorph liver oil, had been taken for the last month prior to the date of writing, with little change in the eruption and no signs of improvement.

COMMENT

Consideration of two factors in this case point to a relationship between the patient's endocrine status and the utilization of vitamin A: (1) Vitamin A in doses of 100,000 units daily (700,000 units per week)

did not deter the development of extensive pityriasis rubra pilaris in a patient who had had minimal signs of this disease for thirty-six years. Vitamin A was quickly effective when it was given parenterally in doses of 200,000 units per week. That the patient's absorption of vitamin A was not defective was shown by the vitamin A tolerance curve. The vitamin A which entered the peripheral circulation, circumventing the influence of the liver, appeared to be more effective than that which first passed through the liver. (2) This patient was observed each week during a period of eighteen months. Synthetic estrogens were given orally and parenterally to control her symptoms of flushing and night sweats, and during this time the signs of pityriasis rubra pilaris steadily increased.

It can be assumed that in this patient administration of estrogen produced an accentuated need of the skin for vitamin A. The oral dose may have been too small, or it may have been rendered less effective during its passage through the liver. Estrogen is known to affect the function of the liver, particularly in regard to the vitamin B complex,[27] and it is possible that the vitamin A was in some way also affected. Conversely, vitamin B complex is necessary for the liver to inactivate estrogen. This might account for the efficacy of the parenterally administered vitamin A, which would escape the portal circulation of the liver. Although no clinical signs of vitamin B deficiency were noticed in this patient, it is not unlikely that such a deficiency did exist.

Of more general interest, however, is the question of the relation of vitamin B deficiency to vitamin A deficiency at the time of puberty. Varied opinions are held in regard to designating phrynoderma as evidence of vitamin deficiency,[28] and it is felt that other factors, aside from the deficit of vitamin A, determine whether or not the changes of follicular hyperkeratosis and xerosis will appear. Frazier, Hu and Chu[24] suggest that when the sex hormones begin to influence the skin during puberty the cutaneous changes of vitamin A deficiency make their appearance. From the reports of cases of nutritional surveys made in India,[29] Africa,[03] Malay[31] and China,[32] it is evident, from the descriptions of angular

27. Biskind, G., and Biskind, M. C.: The Nutritional Aspects of Certain Endocrine Disturbances, Am. J. Clin. Path. **16**:737 (Dec.) 1946.

28. Bicknell, F., and Prescott, F.: The Vitamins in Medicine, ed. 2, New York, Grune & Stratton, Inc., 1946, p. 65.

29. Akroyd, W. R., and Rajagopal, K.: The State of Nutrition of School Children in South India, Indian J. M. Research **24**:419, 1936.

30. Nicholls, L.: Phrynoderma: A Condition Due to Vitamin Deficiency, Indian M. Gaz. **68**:681, 1933.

31. Fasal, P.: Clinical Manifestations of Vitamin Deficiencies as Observed in the Federated Malay States, Arch. Dermat. & Syph. **50**:60 (Sept.) 1944.

32. Frazier, Hu and Chu.[24] Reiss, F.: A Contribution to the Cutaneous Manifestations of Vitamin A Deficiency, Chinese M. J. **50**:945, 1936.

stomatitis, cheilosis and beriberi and from the lists of diets, that these patients were, for the most part, also deficient in the vitamin B complex. Biskind and Biskind[27] have shown that when a vitamin B deficiency is present, the liver is unable to inactivate estrogen. The estrogen appears in excess in the circulation, but the inactivation of androgen continues, so that an estrogen-androgen imbalance results. Estrogen effects on the skin and vaginal mucosa are similar to the changes seen in vitamin A deficiency.[33] The circulating estrogen may act on the epithelium either by direct antagonism to vitamin A or by increasing the metabolic need of the cells for vitamin A. If such be the case, then a deficiency in the B complex may be the deciding factor as to whether or not the signs of phyrnoderma and xerosis appear, and the time of their appearance at puberty is explained. No explanation of the antagonism between estrogen and vitamin A in the skin or vaginal mucosa is apparent from the evidence presented here.

This sequence of events may occur to some degree in such diseases as keratosis follicularis and pityriasis rubra pilaris and thus account for the inconsistent observations in tests for vitamin A deficiency in plasma levels and dark adaptation and may also account for the inconsistent improvement during vitamin A therapy. A better evaluation of this theory might have been possible had the histories been more detailed in regard to the endocrine status of patients with these diseases.

ABSTRACT OF DISCUSSION

Dr. Maximilian E. Obermayer: Dr. Keddie's study is a valuable contribution to the complex problem of vitamin A therapy, for it deals with and suggests an explanation for the inconsistencies of response which have puzzled every dermatologist.

The assumption of a relation of a deficiency of vitamin A to that of the B complex vitamins appears logical. Not only do Dr. Keddie's observations and those of other investigators point in that direction, but it has become almost a dictum that deficiency in a single vitamin hardly ever occurs; in most vitamin deficiencies there is a co-existence of deficiency in one or several other vitamins. This is the case in pellagra and in scurvy, in which the development of hyperkeratotic follicular papules is often observed in the earliest changes and points toward a coexistent deficiency in vitamin A; a similar situation evidently prevails in the so-called vitamin A deficiencies.

An even more important point is the alleged and yet unsolved relation of vitamin A to the sex hormones. If the two substances are either antagonistic or, as Dr. Keddie has suggested, an excess of hormones increases the requirements of vitamin A to a considerable degree, there would be an explanation for some

33. Evans and Bishop.[25a] Burrows.[25b] Rony and Zazon.[26]

of the so far poorly understood observations, as in the observations of deficiency in vitamin A with the formation of follicular hyperkeratoses in pregnancy reported by Rucketts (*Am. J. Obst. & Gynec.* **38**:484, 1939).

It also seems significant that in true vitamin A deficiency, as well as in acne vulgaris, the maximal degree of follicular hyperkeratosis is present during adolescence. Thus, the degree of sexual development appears to be the critical factor in the response of the pilosebaceous structures to a deficiency of vitamin A.

On the other hand, it is difficult to explain, on that basis, the effect of vitamin A in the prevention and treatment of the precancerous degenerative cutaneous changes, such as keratoses, for these conditions ordinarily occur at a time in life when the production of sex hormones is diminished.

Nevertheless, the known fact that estrogen and a deficiency in vitamin B complex affect the function of the liver is important in attempts to explain the inconsistencies of therapeutic response, because this is in correlation with the results of experimental studies by British and South African investigators on the causal connections between hepatic damage and hypersensitivity to light.[34] Such hypersensitivity could, for example, be brought about by damaging the liver through ligation of the common duct. Further studies led to the surprising discovery that absence of a substance which accompanies vitamin A is the critical factor in causation of the hypersensitivity. It has long been known that hepatic cells always contain vitamin A, which is necessary for their normal function. The toxic influence of thyroxin, which leads to the disappearance of glycogen from the liver, can be successfully counteracted by the administration of vitamin A. It is now thought that in the presence of hepatic damage a toxin, probably of intestinal origin, which has escaped destruction in the liver, is activated by sunlight and that treatment successfully directed against the cause of the injury to the liver would eliminate the consequences of hypersensitivity to light. Actually, some British investigators have successfully employed injections of highly refined preparations of natural vitamin A esters containing the active factor which always accompanies such esters in nature. Their work substantiated the theory that it is the absence of this active factor, rather than the disappearance of vitamin A itself from the hepatic cells, which is responsible for the hypersensitivity to light.

By these observations the importance of the connection between damage to the liver and vitamin A metabolism gains new significance, for such damage, sufficient to disturb the process of utilization of vitamin A, may be brought about in many different ways and yet go undetected by present day methods of testing the function of the liver. A disturbance in the balance of the sex hormones, with subsequent dysfunction of the liver and poor utilization of vitamin A, may perhaps be one of the causal factors in acne vulgaris. It is interesting to speculate whether dysfunction of the liver from other causes might be responsible for the tendency to premature degeneration of the skin and the formation of precancerous keratoses, a process in which long-continued exposure to light plays a decisive role. If such correlation were established, a logical explanation for the alleged effect of vitamin A in these disorders would have been found.

One may hope that further studies will be carried out in this direction so that the whole problem of the practically all-important question of pathogenesis of precancerous keratoses may be clarified and practical modes of treatment established.

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34. Adler, A.: Solar Dermatitis in Adults, Proc. Roy. Soc. Med. **36**:284, 1943.

In the meantime I should like to point to the therapeutic effect of the administration of vitamin A in patients with cutaneous diseases characterized by excessive keratinization not limited to the follicular system, that is, calluses, corns, keratoderma and, particularly, common inflammatory dermatoses, such as dry neurodermatitis, which in themselves would not be considered suitable for treatment with vitamin A were it not that some patients have lesions which show an abnormal degree of keratinization and a complete lack of response to standard methods of treatment. In such disorders the administration of vitamin A is of value, but it is highly doubtful that a true deficiency of vitamin A exists. It is likelier that the vitamin, and/or the substances which accompany it, acts as a specific remedy for cutaneous changes, whatever the cause, which are characterized by excessive keratinization.

LICHEN URTICATUS SYNDROME

As a Manifestation of Sensitivity to Bites from Various Species of Arthropods

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CINCINNATI

LICHEN urticatus is probably one of the least understood of the cutaneous diseases of childhood,[1] or, in the words of Walter Highman,[2] "a not very well defined disease of childhood." Howard Fox[1] added that "the disease originally described by Bateman[3] in 1813 has been the source of much confusion, which even persists to a degree at the present time."

At present, lichen urticatus is assumed to be a type of hypersensitive cutaneous reaction of unknown causation. In the literature[4] various factors have been considered, with the variety extending from teething to psychosomatic disturbances. However, there are some definite clinical aspects: first, the clinical picture of the development of the lesions and, second, the seasonal variation. This seasonal variation occurs usually in summer and early fall. The persistent forms of lichen urticatus may last through the winter. It is my impression that the disease in cases observed in clinics in London, England and in Mexico is much severer and more frequent (?) than the disease in cases seen in the United States. Cutaneous testing in patients with lichen urticatus has revealed nothing of value. Cooke[5] indicated that testing gives practically no assistance, since, in his opinion, reagins play little or no demonstrable part in the mechanism. Cooke[5] expressed the belief that when reactions are obtained, they are from the associated atopic disorders and have no "direct demonstrable bearing on the symptoms under investigation."

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1. Fox, H.: Diseases of the Skin in Infancy and Childhood, New York, D. Appleton and Company, 1930, chap. 16.
2. Highman, W., cited by Fox.[1]
3. Cited by Fox.[1]
4. Winkler, 2.: Strophulus, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 1, p. 326.
5. Cooke, R. A.: Allergy in Theory and Practice, Phalidelphia, W. B. Saunders Company, 1947, p. 497.

Walzer[6] indicated that atopy is significant . . . "about 47 per cent of the patients had positive atopic histories." It is curious that in the search for the elusive antigenic factor antigens from insects and the like have not been considered more strongly, since such antigens have been used in allergic conditions.[7] Parents have suggested frequently that bites from mosquitoes and chiggers had initiated the episodes of lichen urticatus.

Bateman[8] in 1814 wrote, "It may be called lichen urticatus; as its first appearance is in irregular inflamed wheals, so closely resembling the spots excited by the bites of bugs or gnats as almost to deceive the observer." Jonathan Hutchinson[3] is reported to have indicated that the disease may be produced by bites of insects. In their discussion on lichen urticatus, Ashby, Wright, Ashby and Roberts,[9] wrote that "in some children fleas and other insects will produce vesicles as well as papules and give rise to more or less constitutional disturbance." In Mexico, Latapi[10] insisted on the reaction from insect bite as the cause of lichen urticatus. He has demonstrated to me such cases caused by bites, especially of the bedbug and the flea.

Some time after the study reported herein was started, the detailed work of Dietrich[11] in Vienna was found. He observed the reaction to the actual bite, "Stichversuchen," of cimices and fleas (Pulex irritans). Of 31 young children with lichen urticatus, 16 had severe (hypersensitive) reactions to cimex bites, and 30 presented severe reactions to flea bites. The lichen urticatus reaction in 21 of these patients was actually caused by fleas, in 3 by cimices, and in 7 by both cimices and fleas.

Twenty-nine cases of lichen urticatus from the dermatologic clinic of Children's Hospital and from private practice have been studied since 1941. In 11 of these 29 cases there was a definite atopic background. In all except 4 cases the eruptions began in late spring and in summer months. In 4 cases the eruptions began in January, September, October and November, respectively. Three of the patients of this group of 4 were definitely atopic, and in the fourth patient the

6. Walzer, cited by Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1938, p. 169.

7. Vaughn, W. T.: Practice of Allergy: Entomogenous Allergy, St. Louis, C. V. Mosby Company, 1938, p. 763.

8. Bateman, T.: A Practical Synopsis of Cutaneous Diseases, ed. 3, London, Longman, Hirst, Rees, Orme & Brown, 1814, p. 13.

9. Ashby, H.; Wright, G. A.; Ashby, H. T., and Roberts, C. B.: Diseases of Children: Medical and Surgical, London, Henry Frowde & Hodder & Stoughton, 1922, p. 675.

10. Latapi, F.: Personal communications to the author.

11. Dietrich, A.: Hautreaktionen nach Ungezieferstichen unter dem Bild eines Lichen urticatus, Arch. f. Dermat, u. Syph. **182**:668, 1942.

lichen urticatus followed scarlet fever at the age of 8 months and persisted for over a year. Two cases of lichen urticatus of the same degree occurred in twins, who were not identical. In 5 patients of the total series, the lichen urticatus definitely followed a reaction to bites in the skin. There was no atopic background in 4 of these persons. The bites were seen by a physician from the onset, and the course of the lichen urticatus which followed was typical. The insects incriminated in the reactions to bites were the mosquito (species?) in 2 cases, the "chigger" (Eutrombicula) in 1 case and the cimex in 2 cases. In 4 patients (3 of these were nonatopic) bites were said by the mother to have started the lichen urticatus, but at the time of examination there was no evidence of any primary reaction to bites. In these 4 patients, then, the reaction can be considered as being to bites from types of arthropods, that in 9 of the 29 patients the probable cause was a reaction to bites of insects and the like. In only 1 of these 9 was the lichen urticatus of a prolonged type of reaction, lasting more than a year. In this patient, the reaction to the bite was described by the mother, so that the case was not considered as of a definite type. Only one third of the patients of this series of 29 had detailed cutaneous testing. A wide variety of positive reactions was obtained, and in none of these were the reactions of any definite value. This supports the contention of Cooke.[5] In 3 patients, cutaneous tests were done with common fly antigen, and in these 3 patients the reactions were negative. No cutaneous testing was done with insect antigens, even in the patients with the "definite" reactions to bites. In several of the patients in whom there was no history of bites, the mother insisted that the patient's going out into the grass would always start this seasonal eruption. Reactions to cutaneous testing, both intradermal and patch testing, with grass antigen were equally negative in these patients. One of the cases of the group in which a "definite" bite had been established was of familial infestation with cimex. The typical bites from cimices were seen on the 3 adults in the family, and the young child of 6 years of age presented, after his typical bites, a generalized, severe and resistent lichen urticatus type of reaction. In the homes of 4 of the children of the group without "definite" reactions to bites, there was detailed employment of insecticides and repellents. These procedures had no effect on the development of new lesions.

Familial scabies was studied in 4 infants and young children, with the possibility that some of the lesions may have been reactions of sensitivity, lichen urticatus type, rather than extension of scabietic lesions. The confusion in the differential diagnosis between scabies and lichen urticatus is well known. These 4 patients were studied in as much detail as is possible in a young child with a generalized

pruritic eruption. Parasites of scabies were isolated from lesions of the extremities, especially from the hand, but lesions on the trunk revealed no parasites. No biopsies were done, however. In 1 child the urticarial lesions were seen preceding the development of the papules. The widespread distribution of the cutaneous lesions of scabies in the young child is well known. Moreover, there may be cutaneous allergy in scabies in the form of associated urticaria and angioneurotic edema. It is suggested, without any definite proof whatsoever, that some of the lesions may be an allergic type of response rather than a direct extension of the lesions of scabies. In 1 child an attempt was made to limit the benzylbenzoate and dichlorodiphenyltrichloroethane (DDT) therapy with bandages only to the hand. However, the general improvement of the child could not be explained entirely as an effect of the treatment on the so-called "primary lesions."

It is suggested also that some of the dermatitis occurring on the back of the neck in children with pediculosis capitis may not always be a bacteride due to the secondary infection or a direct extension, or "toxic" dermatitis or even dermatitis from treatment, but may actually be a type of "localized" lichen urticatus reaction.

In the regions of onchocerciasis in Mexico, reactions to simulium bites were seen in children with typical lichen urticatus reactions.[12] The reactions to bites were studied. Although some persons would present onchodermatitis associated with their reactions to bites, yet other patients would show negative cutaneous results for microfilariae, and it was assumed that their lichen urticatus reaction developed from the bite of the simulium.

No critical studies have been done in this series to explain the persistency of the lesions in lichen urticatus. It would certainly be well to repeat the studies[13] of the development of the lesion of lichen urticatus with biopsies from the initial urticarial phase to the late infiltrated papular reaction. The histologic picture of the difference between the urticarial reaction and the more infiltrated lesion in lichen urticatus may explain some of the persistency of the lesion. The cellular infiltrate is more intense, the vascular damage is severer and the itching reaction, of course, is more prolonged in the lichen urticatus reaction. Similarly, there is more opportunity for secondary infection of the lesions, because of the persistency of the reactions. In 1 patient of this series of 29, definite and casual psychosomatic factors were observed to help to establish the chronicity of the lesion. In none of the older children followed so far, since 1941, has there

12. Goldman, L., and Figueroa Ortiz, L.: Types of Dermatitis in American Onchocerciasis, Arch. Dermat. & Syph. **53**:79 (Feb.) 1946.

13. Frieboes, W.: Grundriss der Histopathologie der Hauthrankheiten, Leipzig, F. C. W. Vogel, 1921, p. 18.

been any suspicion of the development of true chronic prurigo lesions. In several of the atopic patients of this series the concomitant appearance of definite flexural lichenified areas together with the lichen urticatus were observed. Insects are more active, of course, in the warm seasons. However, in México, D. F., Mexico, no special note was made of any seasonal variations of lichen urticatus.

COMMENT

It is obvious that some (how many?) children with the syndrome which is known as lichen urticatus may initiate this reaction by means of the bites of the common type of insects and allied species. The determining factors in these children which produce a generalized allergic response of fairly long duration instead of a primary localized bite type of reaction are certainly not known. Dietrich's[11] work with severe reactions to bites of cimices and P. irritans in lichen urticatus does tend to prove the concept of hypersensitivity in those particular young children with lichen urticatus. His few experiments, likewise, with the young infants showed that hypersensitivity may be acquired after repeated bites. Similarly, hyposensitization may be accomplished also by repeated bites. Dietrich[11] expressed the belief that lichen urticatus no longer occurs when decided decrease in sensitivity to the bites is shown. It seems that it would be possible also to study the lichen urticatus type of response critically by means of appropriate antigens of insects involved. It is curious that in only 2 patients of the group of 9 possible reactors to insect bites was the reaction repeated one more season. In some extremely sensitive patients it may not be necessary to have the actual bite of the insect, but even perhaps endogenous sensitization by means of the emanation or so-called "dust" or debris of the insect.

It is apparent that at the present time the diagnosis of lichen urticatus as a reaction to bites from arthropods can be made only by the definite personal observation of the primary reaction to the bite followed by the dissemination of the characteristic eruption after the primary bite and the actual presence of the insect, when such insects as the cimex, pulex and the pediculus are suspected. The presumptive diagnosis may be made by the observant parent, although this is not reliable. The reaction to insect bite was observed to occur during the spring-summer season and was usually in nonatopic persons. Only critical work with detailed testing, both with prepared antigens and with the actual bite, and observation in a controlled environment will help to elucidate some of the confusion of the syndrome of lichen urticatus.

When bites from insects and the like are suspected in young children with lichen urticatus, detailed search for these offenders

should be made. With modern advances in the chemical control of insects, repellents, especially "NMRI 448" (contains 70 per cent 2-phenyl cyclohexanol and 30 per cent 2-cyclohexyl cyclohexanol), and insecticides, such as dichlorodiphenyltrichloroethane (DDT), octachloro-4,7-methanotetrahydroindane (chlordane or "velsicol 1068") and gamma isomer of 1, 2, 3, 4, 5, 6 hexachlorocyclohexane, should be used efficiently before the older technic of change in environment is advised. However, detailed toxicologic studies of the newer insecticides are still needed.

SUMMARY AND CONCLUSIONS

Of 29 patients with lichen urticatus, definite history and observation of reaction to bites from various species of arthropods as initiating the syndrome was observed in 5 patients and presumptive evidence in 4 patients. These reactors to bites belong, as a rule, to the nonatopic group of patients with lichen urticatus. Personal observations in Mexico have established the fact also that bites from insects and the like may initiate the syndrome of lichen urticatus. The insects incriminated included the fly, chigger, mosquito, flea, cimex and simulium. It is suggested that in some cases of scabies in infants and children a "portion" of the generalized reaction may be a sensitivity response rather than a dissemination of actual infective lesions. Detailed testing with antigens and with the actual insect bite (Dietrich), analysis and environmental control may help to determine the significance of the role of sensitivity from bites of insects and the like in children with the lichen urticatus syndrome.

733 Carew Tower (2).

Clinical Notes

TREATMENT OF FAMILIAL BENIGN CHRONIC PEMPHIGUS

Rapid Improvement with Penicillin Therapy

C. C. Carpenter, M.D., Summit, N. J.

The reports that have been published concerning the treatment of familial benign chronic pemphigus are, for the most part, discouraging.

Because of the repeated observation of the staphylococcus[1] and the occasional presence of short-chained streptococcus[1b] in the vesicles, bullae and crusts characteristic of this affliction, the use of local antiseptics has been the most popular therapeutic approach. Beneficial effects have been noted from the local applications of ammoniated mercury ointment in 1 per cent to 3 per cent concentration,[2] boric acid ointment[2b] and mildly antiseptic wet dressings, including alibour water (water containing zinc and copper sulfates.)[2] Superficial roentgen therapy has been successful in some patients,[3] but in others has proved ineffective.[4] Ultraviolet irradiation produced no improvement in a patient treated by Lynch.[1d]

In an endeavor to achive more permanent results, many types of internal therapy have been tried. The intravenous injections of Staphylococcus aureus vaccine combined with low power roentgen ray therapy kept a patient of Ayres and Anderson[1b] free of lesions for a year. Subsequent recurrences in this same patient could be controlled by repeated intravenous injections of a combined Staph. aureus and Streptococcus viridans vaccine. However, an autogenous streptococcus vaccine did not help a patient of the Haileys.[2b] Lynch[1d] was able to obtain complete healing in his patient with the administration of sulfathiazole for ten days. The value of treatment with this drug is supported by Pinkus and Epstein,[5] who achieved a rapid remission in 1 of their patients with sulfapyridine. High dosage vitamin A therapy has been reported as being useful in 1 patient[5]

1. (*a*) Pels, I. R., and Goodman, M. H.: Criteria for Histologic Diagnosis of Keratosis Follicularis (Darier), Arch. Dermat. & Syph. **39**:438 (March) 1939. (*b*) Ayres, S., Jr., and Anderson, N. P.: Recurrent Herpetiform Dermatitis Repens, ibid. **40**:402 (Sept.) 1939. (*c*) Becker, S. W., and Obermayer, M. E.: Bullous Disease: Bullous Darier's Disease (Pels and Goodman); Familial Benign Pemphigus (Hailey and Hailey); Herpetiform Dermatitis Repens (Ayres and Anderson), ibid. **41**:1170 (June) 1940. (*d*) Lynch, F. W.: Benign Pemphigus (Hailey and Hailey) Treated with Sulfathiazole, ibid. **43**:736 (April) 1941.

2. (*a*) Ayres and Anderson.[1b] (*b*) Hailey, H., and Hailey, H.: Familial Benign Chronic Pemphigus, South. M. J. **33**:477 (May) 1940.

3. (*a*) Ayres and Anderson.[1b] (*b*) Anderson, C. R., in discussion on Ayres, S., and Rogers, J. D.: Recurrent Herpetiform Dermatitis Repens, Arch. Dermat. & Syph. **42**:490 (Sept.) 1940. (*c*) Hopkins, J. G.: Familial Benign Chronic Pemphigus, ibid. **51**:69 (Jan.) 1945.

4. (*a*) Lynch. [1d] (*b*) Hailey and Hailey.[2b] (*c*) Montgomery, R. M.: Familial Benign Chronic Pemphigus, Arch. Dermat. & Syph. **50**:53 (July) 1944.

5. Pinkus, H., and Epstein, S.: Familial Benign Chronic Pemphigus, Arch. Dermat. & Syph. **53**:119 (Feb.) 1946.

and ineffective in another.[4c] Anderson[3b] and Frost[6] expressed the belief that intravenous injections of calcium are beneficial in lessening the eruptive tendency. Among the other internal remedies that have been tried, and which only temporarily altered the progression of this disease, are injections of neoarsphenamine, bismuth compound,[1a] trichophytin,[2b] snake venom, extract of liver, arsenic compound and vitamin K.[3c]

In the general management of patients with this cutaneous disease, Frank and Rein[7] stressed the importance of avoiding superficial trauma, to prevent recurrences, and Montgomery[4c] noted that a change to cooler atmospheres hastened recovery.

As this eruption has been frequently considered to be a form of dermatitis herpetiformis,[8] I thought that penicillin therapy might possibly be of value.[9]

REPORT OF CASES

Case 1.—W. L., a white man aged 39 years, first came under my care in 1932, because of a recurrent cutaneous eruption on the shoulders, neck, axilas and scrotum, which had been variously diagnosed as bullous impetigo and fungous infection. His father had a mild form of this disease all his life, and 2 sisters were known to have had similar cutaneous manifestations.

Except for the recurrences of this eruption, beginning at the age of 19, his general health had been good. However, there have been mild recurrences of epidermophytosis of the feet. All laboratory examinations, including repeated complete blood cell counts, urinanalysis, glucose tolerance test, tests of sedimentation rate and complete chemical content of the blood and Wassermann and Kline tests, have always yielded normal values. The disease, from a biopsy in 1937 (first examination by the late David Satenstein) was considered to be a form of Darier's disease. Dr. Wilbert Sachs reviewed the slide at that time and expressed the belief that it presented observations consistent with epidermolysis bullosa. A subsequent review of the same section in 1942, by Dr. P. A. O'Leary and Dr. H. Montgomery, resulted in agreement on a histologic diagnosis of familial benign chronic pemphigus.

During severe exacerbations of the cutaneous disease in 1937 and 1938, he was seen in consultations with the late Dr. H. J. F. Wallhauser and Dr. G. M. MacKee. The former stated the belief that the patient had an unusual form of epidermolysis bullosa and the latter an aberrant form of pemphigus.

It was consistently observed that this patient was generally worse during the hot summer months, but would also have recurrences in the winter while playing ice hockey. He blamed the wearing of a jockstrap for the formation of new scrotal lesions, and on several occasions new bullae were observed at the cutaneous sites that had been hit by a hockey stick or puck. New lesions on the front of his neck had been produced by the irritation from shaving.

During his naval service in 1944, while he was serving in the heat and humidity of the South Pacific area, a severe exacerbation developed. It was not until

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6. Frost, K., in discussion on Ayres, S., and Rogers, J. D.: Recurrent Herpetiform Dermatitis Repens, Arch. Dermat. & Syph. **42**:490 (Sept.) 1940.

7. Frank, S. B., and Rein, C. R.: Dyskeratoid Dermatosis, Arch. Dermat. & Syph. **45**:129 (Jan.) 1942.

8. Ayres and Anderson.[1b] Anderson.[3b] Pinkus and Epstein.[5]

9. Carpenter, C. C., and Hall, W. H., Jr.: Treatment of Dermatitis Herpetiformis with Penicillin, Arch. Dermat. & Syph. **51**:241 (April) 1945.

he was returned to the cooler climate of a naval hospital in Northern California that any form of local therapy was successful.

From 1932 to 1934 his cutaneous lesions responded satisfactorily to superficial roentgen therapy and the local application of tincture of iodine, silver nitrate, methylrosaniline chloride, alibour water and "quinolor compound ointment" (contains 10 per cent benzoyl peroxide and 0.5 per cent "quinolor" [a mixture of 8-hydroxyquinoline] in a base of equal parts of petroleum and wool fat). At that time he was observed to be hypersensitive to staphylococcus vaccine and was given gradually increasing dosages of staphylococcus toxoid. He remained free of all lesions for a year following this desensitization, and since that time has received three such series of injections, which were successful in suppressing all but minor manifestations for periods varying from seven months to two years. Sulfathiazole was given orally in 1941 for a period of five days, with only moderate success.

In February 1947, this patient returned after an absence of five years. There was minor activity of the cutaneous lesions in his axilla, neck and scrotum, that had been present since the previous summer. Penicillin was given orally, 25,000 units every three hours until 1,500,000 units had been taken, and local therapy was confined to the use of petrolatum. An immediate decided improvement was noted, and all lesions except the most deeply fissured had healed within a week. Subsequent local applications with pencillin ointment and tyrothricin (solution) did not effect any further improvement. Another severe outbreak occurred during the heat of June, and the patient was hospitalized. Combined treatment, with the injection and oral administration of 200,000 units of penicillin daily and the local use of penicillin, 1,000 units per gram of hydrophilic ointment base, produced complete healing of all lesions within five days.

Case 2.—C. L., a white housewife aged 42 years, a sister of the patient in case 1, was seen in January 1947, complaining of a spreading annular eruption on the right shoulder. This was the first manifestation of this cutaneous disease on the glabrous skin, but during the past several years there had been a recurrent fissuring of the anal mucosa, which was believed to be a part of this same disease. Because of the family history, as well as the fact that these fissures had always healed promptly with local antiseptic therapy, no further investigations had been made. Her general health had otherwise been good.

The present eruption had begun ten days previous to examination and was the result of friction produced by a tight bathing-suit strap, worn while on a vacation in Florida. It had started as a small "blister" and had spread eccentrically, in spite of daily applications of a sulfadiazine ointment. When first observed, the area was 2 inches (about 5 cm.) in diameter and had an irregular border of vesicles, bullae and pustular crusts on a raw oozing base. The healed center area was pink and had a superficial scale.

Treatment was started with two daily applications of an ointment containing 500 units of penicillin per gram of hydrophilic ointment base. As a result, the eccentric progression of the border was stopped and the crusted areas healed, but the vesicles and bullae did not disappear. Following this, wet dressings containing 0.3 mg. of tyrothricin per cubic centimeter of distilled water were applied, but the vesicular edge continued to advance. Oral penicillin therapy, with the ingestion of 25,000 units every three hours, was then recommended, with local therapy limited to daily applications of petrolatum. Within four days, and after 750,000 units had been taken, the vesicles and bullae had entirely disappeared, and the involved area of skin had remained entirely well as of the time of writing.

SUMMARY

It has been verified that trauma to the skin and hot weather are predisposing factors in the recurrence of familial benign chronic pemphigus.

It is agreed that some form of desensitization with straphylococcus vaccine or toxoid is helpful in producing remissions of this disease.

Combined internal and local therapy with penicillin is of value in controlling exacerbations.

129 Summit Avenue.

SEVERE REACTIONS TO PENICILLIN

H. H. SAWICKY, M.D.
AND
CHARLES R. REIN, MD
NEW YORK

The oral and topical use of penicillin, in such forms as tablets, lozenges, troches, wet dressings, ointments, sprays and nose and eye drops in the treatment of comparatively minor ailments may sensitize many persons to this valuable antibiotic. Two severe sensitization reactions to penicillin are reported.

REPORT OF CASES

Case 1.—S. B., a white man aged 57, consulted us on July 16, 1946, for chronic furunculosis of ten months' duration. He denied a history of active fungous disease and a personal or family history of allergy. In October 1945, he noted numerous furuncles on his upper extremities. Penicillin ointment was prescribed in November, and, after three weeks of use, an erythematous edematous eruption appeared on the face and neck. The eruption soon became generalized, necessitating hospital care for three months. On July 16, 1946, 300,000 units of penicillin in peanut oil and wax (Romansky formula) was administered intramuscularly for a recurrence of the furunculosis. Within thirty minutes following the injection, the patient presented the picture of "anaphylactic shock." He was apathetic and complained of severe headache, coldness, nausea, vomiting and shaking chills. His face was pinched and his skin pale, with dusky cyanosis of the lips, tip of the nose and ear lobes. His temperature was subnormal; breathing was shallow and sighing, the pulse was barely perceptible, and the blood pressure was 60 mm. of mercury systolic and 0 diastolic. Epinephrine was given subcutaneously and tripelennamine hydrochloride ("pyribenzamine hydrochloride" N.N.R.) administered orally. Within an hour, generalized erythema, edema of the extremities and urticarial lesions on the forehead were noted. The urticaria became generalized and persisted for twenty-four hours, at the end of which time the cutaneous and systemic manifestations of the episode were no longer in evidence.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Post Graduate Medical School and Hospital, Dr. Marion B. Sulzberger, Director.

Abstract of report presented by title at the Conference on Antibiotic Research under the auspices of the Antibiotics Study Section of the National Institute of Health, Washington, D. C., Jan. 31, 1947.

CASE 2.—S. F., a white married woman aged 31, was seen for the first time on March 22, 1947. She gave a history of the onset of sore throat, pain in the back, cough and malaise, March 6, 1947. She denied a history of active fungous disease and a personal or family history of allergy. Treatment with penicillin tablets, 50,000 units every four hours, was started on March 7, and continued, in an irregular manner, until March 22. Because of the persistence of symptoms and a rise in temperature, 300,000 units of penicillin in peanut oil and wax (Romansky formula) was administered intramuscularly on March 15, 16, 17 and 18. During the night of March 18 there was a decided turn for the worse, and two days later the patient was hospitalized, with a tentative diagnosis of septicemia. Examination on March 22 revealed an acutely ill patient, lying in a fixed position in bed and resisting all movements, active or passive. She complained particularly of pains in the muscles, bones and joints. The temperature was 104 F., the pulse rate 120 and the blood pressure 112 mm. of mercury systolic and 75 diastolic. There were generalized giant urticaria, most apparent on the trunk and upper extremities, edema of the upper eyelids and a dusky erythematous edematous scaling eruption on both malar regions. Cervical, axillary and inguinal lymph nodes were enlarged and tender, and the right wrist and right knee joints were hot and swollen. Laboratory observations were as follows: The hemoglobin was 64 per cent, the red blood cell count 3,270,000 and the white blood cell count 21,700, with 81 per cent neutrophils, 13 per cent lymphocytes, 5.5 per cent monocystes, 0 per cent eosinphils and 0.5 per cent basophils. The sedimentation rate (Westergren method) was 57 mm. in fifteen minutes, 102 mm. in 45 minutes and 114 mm. in 60 minutes. Examination of the urine revealed a trace of albumin; the urine was otherwise essentially normal. Results of repeated blood cultures were negative, as was culture of the urine. Culture of material from the throat disclosed Streptococcus viridans predominating.

In arriving at a diagnosis of a severe serum-sickness-like reaction to penicillin, it was necessary to consider and exclude septicemia, acute lupus erythematosus and dermatomyositis.

Treatment with penicillin in all forms was discontinued, and tripelennamine hydrochloride, 100 mg. every four hours, was administered. After forty-eight hours, the eruption showed signs of fading and the patient moved about in bed and stated that the joint and bone pains were less troublesome. On March 29, one week after the cessation of penicillin therapy, the patient was out of bed, free from signs or symptoms. She made an uneventful recovery and was discharged from the hospital on April 2.

The following classification of common reactions to penicillin was previously reported[1]:

A. Toxic Reactions
   1. Intrathecal penicillin reactions
   2. Herxheimer reaction } Not peculiar to penicillin, but common to all potent
   3. Therapeutic paradox } spirocheticides and antibacterial agents

B. Allergic Reactions
   1. Pruritus, urticaria, angioneurotic edema, asthma, serum-sickness-like reaction and anaphylaxis-like reaction (immediate or delayed)
   2. Erythematovesicular desquamating type
   3. Contact dermatitis type
   4. Experimental
      (a) Arthus type
      (b) tuberculin type
      (c) anaphylaxis
      (d) photosensitization(?)

1. Romansky, M. J.: The Current Status of Penicillin Therapy, Veterans Administration Technical Bulletin (TB 10-25), Washington, D. C., Government Printing Office, March 28, 1947.

According to this classification, the condition in case 1 is considered an anaphylaxis-like reaction and in case 2 a serum-sickness-like reaction.

The incidence of allergic reactions of all types following the injection of penicillin in peanut oil and wax (Romansky formula) is about 3 to 5 per cent. It is anticipated that the number of such reactions will rise sharply as more patients become sensitized following the oral and/or topical use of penicillin.

GRANULOMA PYOGENICUM

Report of An Unusual Case

KATHLEEN A. RILEY, M.D.
DURHAM, N. C.

Granuloma pyogenicum is seen commonly in dermatologic practice. Since its first description in 1897 by Poncet and Dor[1] it has been well studied and defined. The original and early investigators called this infection "botryomycosis," because of its similarity to a disease occurring in castrated horses. However, the causation is different, and it is now generally agreed that the cause of granuloma pyogenicum is Staphylococcus aureus. The term "pyogenic granuloma" as Michelson[2] described it included "all sharply circumscribed granulation tissue growths occurring on cutaneous or mucous membrane surfaces and having the appearance of a tumor."

Hartzell[3] first described this condition in America under the name of granuloma pyogenicum. Wile[4] in 1910 summarized the literature to that date with a critical comprehensive review. Michelson in 1925 reported a study of 29 cases, with a complete discussion of the disease process. Since that time there have been only a few scattered reports in the literature.

Granuloma pyogenicum is a rapidly growing granulomatous lesion that usually occurs at the site of an injury. It is usually less than 1 cm. in size. However, there are a few reports of lesions as large as 3 or 4 cm. in diameter. It is usually moist, fleshy, mushroom-like and bright red, bluish red or brownish red. At times the surfaces may be ulcerated, presenting a purulent discharge. Granuloma pyogenicum frequently occurs on the hands, arms and face, but occasionally may occur on mucous membranes. However, no part of the body seems to be immune. All ages and both sexes are affected about equally. The subjective symptoms may be insignificant, although hemorrhage is common. Pain, if present, is mild, but itching may be extreme.

The typical histologic picture is that of an infected angioma. Characteristically it is a pedunculated lesion showing numerous capillaries and newly formed vessels densely infiltrated with leukocytes which are predominately polymorphonuclear in character.

From the Division of Dermatology and Syphilology, Department of Medicine, Duke University School of Medicine, Durham, N. C.

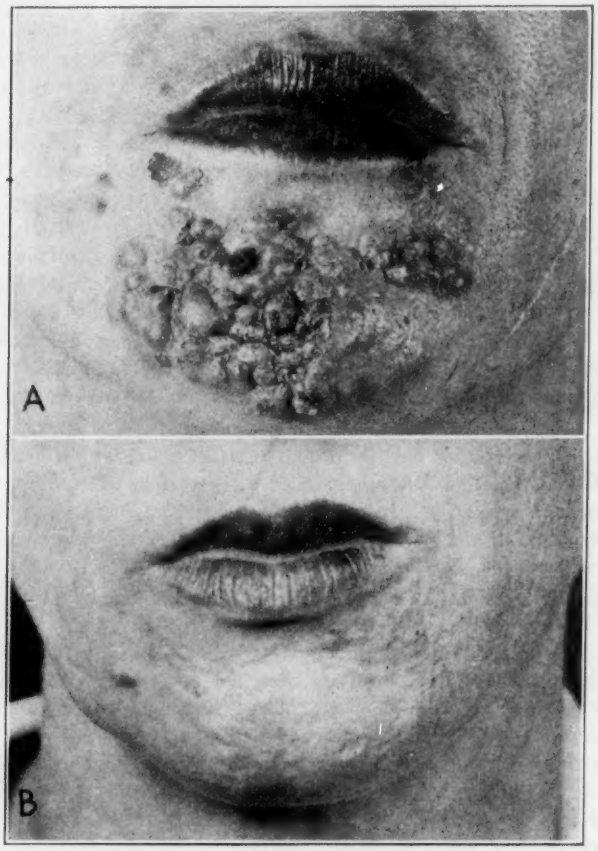
1. Poncet, A., and Dor, L.: Botryomycosis humaine, Rev. de chir. **18**:996, 1897.

2. Michelson, H. E.: Granuloma Pyogenicum: Clinical and Histologic Review of Twenty-Nine Cases, Arch, Dermat. & Syph. **12**:492 (Oct.) 1925.

3. Hartzell, M. B.: Granuloma Pyogenicum, J. Cutan. Dis. **22**:520, 1904.

4. Wile, U. J.: Granuloma Pyogenicum, J. Cutan. Dis. **28**:662, 1910.

The prognosis is usually good if the lesion is completely removed by electrodesiccation or freezing. Since the advent of the use of sulfonamide drugs, there have been reports by Allison[5] and Drummond[6] of response to systemic administration of sulfathiazole in a dosage of 4 Gm. per day. Treatment with roentgen rays has also given excellent results. However, if the lesion is not completely destroyed recurrence is common. I feel that the case presented is such an unusual one that it warrants reporting.



A, appearance of the lesions before treatment. *B*, appearance of the chin after treatment.

REPORT OF A CASE

L. M. F., a 41 year old white married woman was seen first at Duke Hospital on Jan. 21, 1946, with a chief complaint of a cutaneous eruption on her chin.

5. Allison, J. R.: Granuloma Pyogenicum Treated with Sulfathiazole: Report of Case, Arch. Dermat. & Syph. **45**:579 (March) 1942.

6. Drummond, A. C.: Unusually Large Multiple Granuloma Pyogenicum of the Scrotum Treated with Sulfathiazole, Urol. & Cutan. Rev. **47**:515, 1943.

Present Illness.—Four weeks previously a hard painful erythematous nodule had developed on her chin. This was surrounded by several similar smaller lesions, all of which contained a small amount of pus. She had been treated with a penicillin ointment, but the lesions had continued to spread.

Family and marital histories were noncontributory.

Physical Examination.—On the chin was a cauliflower-like mass of grouped papular lesions, about 5 cm. in diameter. The lesions were erythematous, soft, shiny and spotted with crusts and a pustular exudate (*A* of the figure). Except for the presence of the cutaneous lesions, the physical examination revealed the patient to be essentially normal.

Laboratory Observations.—The peripheral blood observations were normal, with a hemoglobin content of 13.9 Gm., red blood cells 4,650,000 and white blood cells 11,450; the differential count showed 59 per cent polymorphonuclear cells, 4 per cent eosinophils, no basophils, 10 per cent monocytes and 27 per cent lymphocytes. Kahn, Kline, Wassermann and Mazzini reactions were negative. Culture of the lesion revealed hemolytic and nonhemolytic S. aureus. The histologic picture was that of granuloma pyogenicum.

Course.—Potassium permanganate compresses (solution of 1 to 4,000) were applied to the chin, one hour three times a day, followed by benzalkonium chloride in solution of 1 to 1,000. The patient was given 10,000 units of penicillin every three hours for the first ten days of hospitalization. She was then given 1 Gm. of sulfadiazine four times a day. On the fourth hospital day the entire lesion was electrodesiccated, with the patient under "pentothal sodium" (sodium 5-ethyl-5-(1-methylbutyl) thiobarbiturate) anesthesia. After fourteen days the patient was discharged, with the lesion decidedly improved.

The patient was followed up in the outpatient department for six months. During this time several small new papular lesions appeared, and on each return visit they were electrodesiccated and touched with 50 per cent trichloroacetic acid solution. The patient continued to use the benzyltrialkonium chloride on the lesions three times a day and applied penicillin ointment three times a day. The patient also continued to take 0.5 Gm. of sulfadiazine four times a day. In June, six months following the onset of the disease, there was no active process and the chin appeared normal except for some erythema at the site of the previous lesions (*B* of the figure).

COMMENT

This patient presents the usual history and course of granuloma pyogenicum. However, it is interesting, because despite the unusually large size and number of lesions a good result was obtained, from a curative as well as from a cosmetic point of view. The patient's chin was not scarred or marred, and no "cover-up" or plastic surgery was required. Ten months after treatment was discontinued, there was no recurrence of the lesion.

Obituaries

WILLIAM THOMAS CORLETT, M.D.
1854—1948

Dr. William Thomas Corlett, the oldest living member and honorary member of the American Dermatological Association, Inc., died on June 11, 1948, following a cerebral vascular accident.

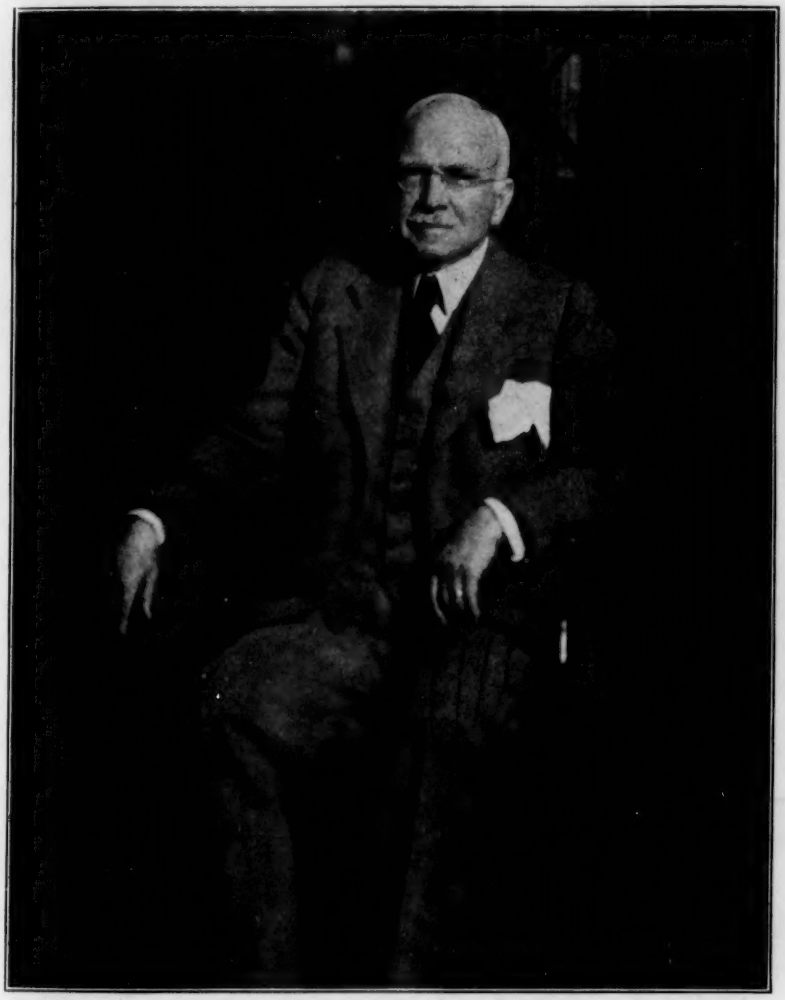
Dr. Corlett was born on a farm in Orange Township, Cuyahoga County, Ohio, April 15, 1854, a son of William and Ann (Avery) Corlett. In his boyhood and young manhood he knew the meaning of hard toil. He was the thirteenth William Corlett in direct descent from his Isle of Man ancestors, family records going back to 1500. He graduated from Chagrin Falls Academy, then entered Oberlin College and received his medical degree in 1844 from Wooster University Medical Department, now a part of Western Reserve Medical School.

He then started the practice of medicine and was named Demonstrator of Anatomy in his Alma Mater. However, he was not satisfied with the outlook and consulted several well known medical men in regard to the postgraduate study of diseases of the skin and syphilology. They all told him that he was crazy, that he would starve to death. Nevertheless, he borrowed money at 8 per cent per annum from an uncle and went to London, studying at the London Hospital, receiving his L.R.C.P. (London) at The Royal Colllege of Physicians in 1881; later going over to l'Hôpital St. Louis, in Paris, for a period. He studied under such men as Jonathan Hutchinson, Sir Frederick Treves, Tilbury Fox, Stephen MacKenzie and Crocker. He numbered Sir Malcolm Morris among his life-long friends and fellow students.

In 1882 he returned to Cleveland as the first dermatologist in that part of the country. He was named Lecturer in Skin Diseases in the Medical Department of Wooster University and opened the first dermatologic clinic in Northern Ohio. The next year he was made full professor. In 1885 he went to Western Reserve University as lecturer and three years later was made full professor, a chair which he held until his appointment as professor emeritus in 1914. His chair of dermatology and syphilology is one of the oldest west of the Alleghenies. He was appointed visiting dermatologist to various hospitals in Cleveland.

The great smallpox epidemic in Cleveland and Northern Ohio in 1899 and 1900 brought out his highest qualities as a physician and public servant. He was an observant student and saw practically every case

occurring in the Cleveland area and Northern Ohio. Moreover, too little was known of the subject at the time, and he acquired a large collection of photographs of the disease in all its stages. This is the basis on which his monograph on acute exanthemas was based. It was con-



WILLIAM THOMAS CORLETT, M.D.
1854 - 1948

sidered an authoritative volume of its time and received international notice. He was invited to give the annual oration to the Dermatological Society of Great Britain and Ireland in 1903, his address being on smallpox. Through the years he made many return trips to the various

clinics in England and on the Continent, as well as to the Caribbean Sea and the shores of South America and to Hawaii.

In 1936 he presented the Corlett Room to the Cleveland Medical Library. Many American and foreign dermatologists are acquainted with this gem containing the bound volumes of current journals on dermatology and syphilology, as well as many other precious volumes of the past devoted to this specialty. The room is also of great interest to medical students and younger dermatologists because of the large number of very creditable oil portraits of American, French, German and English dermatologists and scientists of a past generation. It is a worthy memento of the man to his fellow men.

Despite a busy life in his work and teaching, Dr. Corlett found time to write many articles on his specialty and volumes on various subjects as well: "The Exfoliative Dermatoses" in Morrow's "System of Dermatology," volume 3, 1894; "The Vegetable Parasitic Diseases of the Skin" in Bangs and Hardaway's "American Textbook of Genito-Urinary and Skin Diseases," 1898; "The Acute Infectious Exanthemata," 1901; "Purpura, Pompholyx and Pellagra" in "Reference Handbook of the Medical Sciences," 1903; "Lichen, Lentigo, and Granuloma Annulare" in the 1905 edition of the "Reference Handbook of the Medical Sciences"; "The American Tropics," 1908; "The People of Orrisdale and Others," 1917; "Reminiscenses," 1920; "Medical Miscellany, Mostly Historical," 1932; "The Medicine Man of the American Indian and his Cultural Background," 1935, and "Afterglow Meditations," 1943, an epic poem in blank verse, composed and published after the death of his beloved wife, Amanda Leisy Corlett, who had done so much in encouraging him through his long career.

In addition to honors showered on him by his local medical societies, Dr. Corlett was a Fellow of the Royal Society of Medicine, Great Britain, and a Corresponding Member of the British Association of Dermatology and Syphilology. He was a delegate to the American Public Health Congress in Mexico City in 1892, a delegate to the International Medical Congress in Rome in 1894 and in London in 1913 and a delegate to the International Dermatological Congress in London in 1896. He was a Fellow of the American Medical Association and of the American Association for the Advancement of Science. He served as Secretary and later as President of the Section on Dermatology and Syphilology of the

American Medical Association and was a member and one time President of the American Dermatological Association, Inc., as well as an honorary member in his later life. He was an honorary member of the New York Dermatological Society and served for a long term of years on the editorial board of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. In 1943 the honorary degree of Doctor of Humanities was conferred on him by Western Reserve University.

His memory will be treasured by his students and revered by his associates and colleagues, but long after the man himself is forgotten his Corlett Room in the Cleveland Medical Library will serve as an inspiration to future generations of medical men and dermatologists.

HAROLD N. COLE, M. D.

FELIX PINKUS, M.D.
1868—1947

Dr. Felix Pinkus died on Nov. 19, 1947, at the home of his son, Dr. Hermann Pinkus, in Monroe, Mich. He was born in Berlin, Germany, on April 4, 1868, where he lived and practiced the greater part of his life. Dr. Pinkus came to America in 1941 and made his home here until his death.

He attended the universities of Berlin and Freiburg, receiving the M. D. degree from the latter institution in 1893. He showed an interest in comparative anatomy early in his medical career. His graduation thesis was on the subject of the cranial nerves of Protopterus annectens, in which he described the nervus terminalis, formerly discovered in sharks by the Berlin anatomist Gustav Fritsch, and later verified by others through the whole series of vertebrates, including man.

In his early years he worked in the laboratories of Paul Ehrlich on problems related to diphtheria antitoxin and in the institute of Robert Koch, and he carried on research under Engelmann and Fritsch in the physiologic institute in Berlin.

His dermatologic training included an assistantship in Breslau under Albert Neisser, where he began his work on the normal anatomic structure of the skin, a task which he continued throughout his life. Because of his mastery of that subject, he was asked to write on the anatomy of the skin for Jadassohn's "Handbuch," a truly notable contribution. He also contributed a most remarkable chapter on embryology of the skin for Keibal and Mall's "Manual of Human Embryology." In Breslau he worked on leukemia, a subject in which he was particularly interested, because of his association with Ehrlich, whose early studies on staining the blood he had the opportunity of observing at first hand. Dr. Pinkus continued his dermatologic training in Bern, Switzerland, with Jadassohn, and did postgraduate work at the Hospital St. Louis in Paris. He contributed to many medical encyclopedias and wrote a book on the hair and a textbook on dermatology. He also edited a reference book on syphilis.

Dr. Pinkus made a hobby of studying the phylogenetic origin, structure and pathologic changes of the hair and nails, and his knowledge of those structures and their diseases was equaled by none. He discovered an organ which he called Haarscheiben, a nerve disk, near the hair root, and also a muscle belonging to the hair follicle, which is arranged at right angles to the muscle arrector pilorum. He worked out the method

of nail growth by studying the structure of the horse's hoof and was able definitely to demonstrate the likenesses.

Dr. Pinkus practiced dermatology in Berlin from 1898 to 1938. He was a professor of dermatology at the University of Berlin and for twenty-five years was director of the Reinichdorf Women's Hospital. Here he observed, treated and studied syphilis on a material over which he had absolute control. He was one of the first to use Ehrlich's "salvarsan" (arsphenamine) and made one of the first complete studies of arsenical dermatitis, following the use of that drug. It is not necessary to cite his many medical papers. His recognition and description of the disease which is associated with his name, lichen nitidus, is perhaps best known to us. His contributions to medical literature numbered one hundred and fifty.

Dr. Pinkus' family came from Silesia and later settled in Berlin. His father established a sales agency for linens; one brother, George, was a chemist; his other brother, Eugene, was a manufacturer of fine surgical instruments. Dr. Pinkus' son, Hermann, and his daughter, Luise, are both physicians. There is one surviving grandchild.

His intellectual attainments alone could never have given him the particular characteristics which made him so decidedly different and likeable as a man. They might be summed up as simplicity, an almost childlike innocence, together with great intelligence and integrity. He usually appeared preoccupied, but never seemed to miss anything. Actually, he always listened intently to the conversations and problems of others, and he possessed a sensitivity which made it easy for him to be in accord with the situation at hand. He had artistic ability, so well demonstrated by his color sketches and his keen interest in the creative arts. His crayon illustrations on the black board, when giving a medical lecture, were a delight to his audiences.

Felix Pinkus was noble and gallant, and, although he had encountered many difficulties in his life, he was never self pitying nor vindictive. He was understanding and forgiving. His modesty and retiring nature prevented his seeking many offices and honors which he could have had. In addition to his membership in the Berlin Dermatological Society, he was a corresponding member of the French Dermatological Society. He also was a member of the Detroit Dermatological Society and was elected an honorary member of both the Minnesota Dermatological Society and the Society for Investigative Dermatology. In 1946 and again in 1947 he was invited to deliver a series of lectures on dermatologic subjects and histopathology before the staff of the Division of Dermatology at the University of Minnesota. On each occasion he gave freely from his great store of knowledge and endeared himself to all who came in contact with him.

He enjoyed a good cigar and a bottle of rare Rhine wine, and to visit with him after a good meal was like attending a performance of David Warfield in "The Return of Peter Grimm." Here was a man who had known Virchow, Koch and many others whose names are almost legendary, but he could also discuss the virtues and contributions of more recent eminent men, such as Darier, Jadassohn and Arndt. He particularly admired Ehrlich, whom he considered to be the only real genius he had known. His connection with Ehrlich was intimate, both scientifically and personally. Ehrlich married Pinkus' cousin, Hedwig Pinkus. A biography based on his personal knowledge and on Ehrlich's diaries and notebooks was the task of his last two years. It is a pity that death interfered with this work. for the interest of all dermatologists in the biography of the inventor of arsphenamine, especially when written by Felix Pinkus, would have been great.

We who knew Dr. Pinkus well regarded him with admiration and sincere affection. He had all the qualities of a great human being. To have had the privilege of learning from him should inspire students to continued search for the explanation of many obscure dermatologic problems. His lectures were erudite and original, for he so often said, "I record only what I myself have seen, not what I have been told." His histologic sketches and his lecture notes constitute another great work well begun, but ended all too soon.

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